Pilot Study of the Contour Neurovascular System™

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Study Information	
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Device Name	**Contour Neurovascular System™**
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1 Overview

This document is a clinical investigation plan (CIP) for a Pilot Study of the Contour Neurovascular System™. The Contour Neurovascular System is an investigational device.

2 Pilot Study Synopsis

Study Title	Pilot Study of the Contour Neurovascular System™
Device Name	Contour Neurovascular System™
Primary Objective	To collect and report the safety variables data of the Contour Neurovascular System™
Secondary Objective	To collect and report the efficacy variables data of the Contour Neurovascular System™.
Design	Prospective, single arm, multi-centre study
Assigned Intervention	Endovascular treatment with the Contour Neurovascular System™ for an unruptured intracranial aneurysm (IA)
Target Patient Population	Patients with unruptured IAs suitable for treatment with the Contour Neurovascular System™ and who meet study eligibility criteria
Primary Variables	Safety: Safety variables are the occurrence and frequency of adverse events (AE)s, adverse device effects (ADE)s, serious adverse events (SAE)s, serious adverse device effects (SADE)s and unanticipated serious adverse device effects (USADE)s. Specific AEs associated with this procedure that shal be evaluated include but are not limited to: blood vessel perforation or rupture, unintended thrombosis, adverse tissue reaction, infection, and hematoma formation, and major ipsilateral stroke/subarachnoid hemorrhage (SAH) or death due to neurologic cause within six (6) months after treatment.
Secondary Variables	Efficacy: Efficacy variables are related to the ability of the device to emobolize the aneurysm and shall be analyzed relative to the baseline visit. The variables to be collected and reported shall include but are not limited to: Angiographic and/or magnetic resonance imaging (MRI)/MR angiogram (MRA) assessment of aneurysm occlusion including evaluation of occlusion grade, parent vessel patency, physical positioning, occlusion durability, and any device migration.
Sample Size	A maximum of forty-five (45) subjects
Number of Sites	A maximum of five (5) clinical study sites
Study Visits	Baseline, procedure, six (6) weeks, six (6) months, and one (1), two (2), three (3), four (4), and five (5) years

Study Duration	Projected to be at least 5 ½ years, including enrolment (assumes 6 months for enrolment)

3 List of Acronyms

The following list provides acronyms used in this document and their meaning:

1. AE - adverse event
2. ADE - adverse device effect
3. CIP – clinical investigation plan
4. CRF – case report form
5. CRO - contract research organizations
6. CT - computed tomography
7. CTA - computed tomography angiography
8. CTA – clinical trial agreement
9. DPW - detachable pusher wire
10. EC – ethics committee
11. GCP - Good Clinical Practice
12. IA - intracranial aneurysm
13. IC – informed consent
14. ICF – informed consent form
15. ID - identification
16. MC – microcatheter
17. MR - magnetic resonance
18. MRI – magnetic resonance imaging
19. MRA – magnetic resonance angiogram
20. mRS - modified Rankin Scale
21. PI - Principal Investigator
22. SADE – serious adverse device effect
23. SAE - serious adverse event
24. SAH – subarachnoid haemorrhage
25. TOF- time-of-flight
26. USADE - unanticipated serious adverse device effect
27. WOS - WEB occlusion scale

4 Introduction

Intracranial aneurysms (IA)s are an important medical condition that can lead to substantial morbidity and mortality. An IA is caused by a weakness in the wall of a cerebral artery, which leads to dilation or expanding of the blood vessel. Untreated, IAs can rupture, a condition known as subarachnoid haemorrhage (SAH). Roughly 30% of patients with SAH due to IA rupture die; of survivors, roughly 30% are left with significant neurological deficits.[1] When large, IAs may also cause neurological symptoms resulting from “mass effect.” Common symptoms include double vision, loss of visual fields, headache and other cranial nerve problems.

Current treatment for IAs is provided in two settings: ruptured and unruptured IAs. When ruptured, the clinical goal is to stabilize the patient and reduce the risk of rebleeding from the IA. Surgical treatment involves opening the skull and placing clips or other devices over the offending IA. Endovascular treatment typically involves placement of coils into the target aneurysm through a catheter.
Coil embolization of IAs is a well-established therapy. In ISAT, a large randomized comparison of surgical and endovascular treatment of IAs, endovascular treatment was shown to have a lower rate of death or dependence at one year compared to surgical treatment.[2] Ten-year follow-up from ISAT showed that rebleeding from the target IA was uncommon but slightly higher in the endovascular group (p=.02). However, the rate of death or dependence was lower in those treated with the endovascular approach.[3]

Incomplete occlusion of the target IA is associated with increased risks of aneurysmal bleeding. In CARAT, a large US clinical trial, in comparison to patients with complete IA occlusion, patients with 91-99% occlusion had a 2.9-fold increased risk of aneurysmal bleeding; relative risks of rebleeding with residual neck (70-90% occlusion) and partial occlusion (<70%) were 2.9 and 21.7, respectively.[4] For this reason, clinicians attempt to occlude the target IA as completely as possible.

Currently, the most commonly provided endovascular therapy for IAs is coil embolization. Despite the high prevalence of its use, coil embolization is substantially restricted due to geometric limitations and target IA access. Moreover, complete occlusion of the target IA is relatively uncommon; in a large randomized trial of coil embolization, complete occlusion of the target IA at 6-month follow-up was seen in only about 30% of cases.[5]

It is commonly accepted that large IAs or those with a neck size >4 mm are more difficult to completely occlude with embolization coils. Wide-necked IAs are especially difficult to treat, as the geometry of the IA does not allow coils to stay in place. Adjunctive devices to improve coil embolization in wide-necked IAs are available. Balloon catheters may aid the clinician in packing the IA with coils and several intravascular stents are now commercially available. These stents are placed in the parent artery adjacent to the target IA; stent struts help to hold coils in place inside the target IA. Unfortunately, few studies are available to estimate the relative increase in complete occlusion rate provided by these adjunctive devices. Even more challenging is the treatment of wide-necked IAs located at arterial bifurcations. Placement of intracranial stents in a variety of configurations has been associated with a significantly higher risk [6,7].

Incomplete occlusion has additional risks, including growth of the IA and reopening related to continued pulsatile blood flow into the IA. Moreover, coils can become compacted and regress into the dome of the IA, resulting in further filling at the IA neck. In addition to exposing patients to bleeding risk, incomplete IA occlusion is also associated with the need for surveillance, which is stressful for patients. More importantly, these patients may need another embolization. Retreatment procedures can be complex and not always successful, thereby exposing the patient to further risk.

Recently, a new set of devices for IA treatment have become available. These devices, called flow diverters, are stents placed in the parent artery. Flow diverters have a mesh component that retards the flow of blood from the parent artery into the IA fundus. Stasis of blood in the fundus induces IA thrombosis, which achieves the goal of preventing pulsatile flow into the IA. The mesh component of flow diverters has also been shown to serve as a scaffold for endothelial growth,[8] which can promote permanent occlusion of the target IA. These two components (flow disruption and scaffolding for re-endothelialisation) distinguish flow diverters from standard coils embolization. For large (>10 mm in maximum dimension) and giant (>25 mm) IAs, flow diverters have been shown to have high complete occlusion rates.[9] Most flow diverting devices are placed into the parent artery, requiring the patient to take antiplatelet agents (aspirin and clopidogrel) for prolonged periods. This can be a significant limitation, which precludes their use in the acute setting of aneurysm treatment.

Another group of devices used in endovascular treatment of IAs, intra-saccular flow disrupters, do not require antiplatelet therapy as a prerequisite. These devices are placed in the IA and their mechanism of action is to disrupt the intra-aneurysmal blood flow and subsequently create intra-aneurysmal (and intra-device) thrombosis. The Contour Neurovascular System™ device (Cerus Endovascular Limited, Oxford, UK) is designed to be a flow disruptor that is placed into the IA sac, and does not require the use of antiplatelet therapy. The Contour Neurovascular System™ device is composed of a double layer of 72-wire platinum core Nitinol braid mesh heat-set into a concave shape. The device is delivered through a 0.027" microcatheter into the IA fundus and is placed at the IA neck. It is designed to disrupt blood flow into the IA and to act as a scaffold upon which endothelial cells can grow. These two mechanisms of action may increase the likelihood of complete IA occlusion compared to embolization coils.

Other intra-saccular flow disruptors, such as the WEB™ Aneurysm Embolization System (Sequent Medical, Aliso Viejo, CA) and LUNA Aneurysm Embolization System (Medtronic, Inc., Irvine, CA), have been developed and have CE mark approval. Despite working in principle in the same way as the Contour Neurovascular System™, these other devices have demonstrated certain limitations in their use [10, 11]. For example, certain inherit properties of the WEB necessitates selected geometric "matching" of the device to the overall aneurysm shape. Failure to do so has led the device to migrate distally in the aneurysm or to compacting/foreshortening of the device with subsequent neck recanalization. It has become increasingly clear that accurate correlation of the shape of the WEB to the aneurysm is of critical importance and may not always be possible. Accordingly, there is a need to address these limitations and further improve the performance of intra-saccular flow disruptors.

This CIP describes a pilot study for the Contour Neurovascular System™ for the treatment of unruptured IAs.

5 Investigational Device Description

5.1 Implant and Delivery system

The Contour Neurovascular System™ is comprised of the Contour Neurovascular System™ implant (hereafter called "Contour implant"), which is pre-attached to a detachable pusher wire (DPW), and an Introducer. The DPW facilitates the delivery of the Contour implant through a microcatheter (MC) and into the aneurysm. All devices are provided sterile and non-pyrogenic, and are for single patient use only.

The Contour Neurovascular System™ consists of a self-expanding, concave shaped device (implant) comprised of a double layer mesh made from nickel-titanium with a platinum core. See **Figure 1** below. The implant also has a platinum marker for additional visualization during the procedure. The preattached DPW has a composite stainless steel and polymer construction. The Introducer is a single lumen polymer tube that is used to constrain the Contour implant during introduction into the MC hub. The Contour implant body and proximal marker can be visualized under fluoroscopy.

Given the platinum core of the device's mesh and the platinum marker, the Contour implant is radiopaque and delivered into the target IA under fluoroscopic guidance using standard endovascular techniques and a commercially available microcatheter. The implant is electrolytically detached from the DPW using a commercially available detachable coil power supply.

The Contour Neurovascular System™ is provided sterile with an Introducer preloaded onto the DPW shaft just proximal to the implant. Refer to the Instructions for Use for additional information.

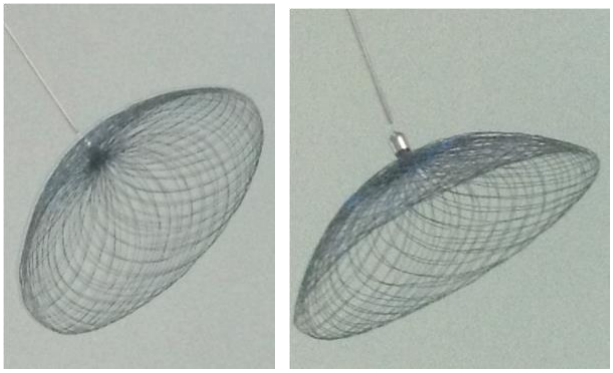

Figure 1. Contour Neurovascular System™ implant

5.2 Device Manufacturing Overview

The Contour Neurovascular System™ is manufactured by Cerus Endovascular Inc. which is ISO 13485 certified. Components are supplied and sterilization is performed by suppliers of Cerus Endovascular. The approved suppliers are managed by Cerus personnel in accordance with Cerus quality system procedures and component/device specifications. Ethylene oxide sterilization processing is performed by an ISO 13485 registered contract sterilizer. The sterilization process is performed in conformance with applicable standards.

6 Risks and Benefits

6.1 Risks

Risks of Contour Neurovascular System™ device are similar to those identified during commercially available endovascular IA treatment and are well known. Risks, some of which could be fatal or cause severe neurologic deficit, are listed below:

- Aneurysm rupture causing intracranial haemorrhage
- Injury to parent artery causing thrombosis or haemorrhage
- Distal embolization of particles or blood clot causing stroke
- Parent artery vasospasm
- Parent artery dissection
- Symptoms related to aneurysm occlusion
- Aneurysm recanalization
- Infection
- Device migration causing incomplete occlusion, haemorrhage or ischemic stroke
- Cerebral angiography risks such as allergic reaction to contrast media, radiation exposure, and groin femoral artery bleeding/infection.

  Note: The radiation dose from a cerebral angiogram is equivalent to about 2 years of background radiation and increases the risk of inducing cancer to 0.025% (1 in 4,000)

For a complete list of risks, see the device's Instructions for Use. There may be unknown risks.

6.2 Anticipated Benefits

As previously described, recent results from the use of existing intra-saccular flow disruptor devices have shown a risk of compaction and neck regrowth. The Contour Neurovascular System™ device is designed to increase the likelihood of complete IA occlusion. Complete IA occlusion may reduce the risk of subsequent IA rupture including in difficult to treat wide-necked or bifurcation aneurysms.

7 Investigational Protocol

7.1 Design

Single-arm multi-centre prospective clinical trial.

7.2 Objectives

The primary objective of this study is to collect and report the safety variables data of the Contour Neurovascular System™.

The secondary objective is to collect and report the efficacy variables data of the Contour Neurovascular System™.

7.3 Target Patient Population

The target patient population is patients with unruptured IAs requiring endovascular treatment. Unruptured IAs are common and those that have wide necks (neck >4 mm) are difficult to treat with standard coil embolization.

7.4 Screening

Patients will be screened for participation through standard methods. Typically, patients with IAs are referred to neurovascular clinicians for evaluation and treatment of IAs discovered routinely or because of an IA rupture.

Screening involves a clinical evaluation and a review of appropriate imaging which typically includes a computed tomography angiography (CTA) and subsequently a cerebral angiogram, which are all standard of care for patients who have been diagnosed with an IA. It is recommended that the screening angiogram include the acquisition of a 3D rotational angiogram of the aneurysm and parent vessel for proper evaluation of the anatomy.

7.5 Eligibility

To participate, **patients must meet all inclusion criteria and no exclusion criteria listed below**. The available sizes of the Contour implant as well as the aneurysm dimensions are provided in **Table 2,** and the Aneurysm dimension definitions are provided in **Figure 2** below. All patients must sign a studyspecific consent form prior to the study procedure. Final qualification will occur during the study procedure due to the need for confirmation of IA appropriateness with cerebral angiography. The patient is enrolled and is considered a study subject only when the patient is fully qualified and at least one investigational device has been placed into the patient's body. If at the onset of the study procedure, the patient's IA is not deemed appropriate by the investigator and no investigational device has been placed

into the body, the patient will be excluded from the study and treated outside of the study per the investigator's usual practices. The following provides examples of patient enrolment scenarios for the study:

1. The patient is not considered enrolled in the study: at the onset of the procedure, the investigator determined the patient's IA was not suitable for treatment with the investigational device, thus, no attempt was made by the investigator to place the investigational device. The patient will be treated outside of the study per the investigator's usual practices.

2. The patient is considered enrolled in the study: at the onset of the procedure, the investigator determined the subject's IA was suitable for treatment with the investigational device. The investigator attempted but was unable to place the investigational device within the IA and the subject required alternative treatment. The subject is considered enrolled for the purposes of the study but will only be followed through the six-week visit.

3. The patient is considered enrolled in the study: at the onset of the procedure, the investigator determined the subject's IA was suitable for treatment with the investigational device. The investigator successfully placed the investigational device within the IA. The subject is considered enrolled for the purposes of the study and will be followed for the duration of the study.

4. The patient is considered enrolled in the study: at the onset of the procedure, the investigator determined the subject's IA was suitable for treatment with the investigational device. The investigator successfully placed the investigational device within the IA. In addition, the subject required and received further treatment with another endovascular device(s). The subject is considered enrolled for the purposes of the study and will be followed for the duration of the study.

Table 1. Study eligibility criteria Patients must meet all inclusion criteria and no exclusion criteria listed below

Inclusion criteria	**Exclusion criteria**
1. Age 18-80 years at screening 2. Unruptured saccular IA in the anterior or posterior circulation with dimensions consistent with Table 2 3. IA appears suitable for Contour Neurovascular System™ device 4. Patient has the necessary mental capacity to participate and is willing and able to participate in the study for the duration of the study follow-up and is able to comply with study requirements Patient able to understand and sign a study-specific informed consent form	1. Ruptured IA 2. Any other IA that requires treatment in the next year 3. IA width >8.5 or <2 mm 4. IA neck >8 or <2 mm 5. IA embolisation would most likely cause stroke 6. Target IA contains other devices/implants (e.g., coils) 7. Inability to access the target IA with the microcatheter 8. Any congenital or iatrogenic coagulopathy 9. Platelet count <50,000/microliter 10. Known allergy to platinum, nickel or titanium 11. Known allergy to contrast agents 12. Stenosis of the target IA's parent vessel >50% 13. Taking daily aspirin or other platelet inhibitor (clopidogrel or equivalent) other than for the target aneurysm 14. Taking any anticoagulants (e.g., warfarin) 15. Abnormal clotting parameters 16. Pregnant, breastfeeding or planning pregnancy in the next 2 years 17. Other medical conditions that could increase the risk of neurovascular procedures (e.g., liver failure, cancer, etc.) or ability to comply with study requirements 18. Participating in another study with investigational devices or drugs

Table 2. Contour Neurovascular System™ and aneurysm dimensions

REF (Catalogue Number) – Diameter	**Aneurysm Neck (mm)***	**Aneurysm Width (mm)***
CNS05 – 5 mm	2.0 - 3.0	2.0 - 3.5
CNS07 – 7 mm	3.0 - 5.0	3.0 - 5.5
CNS09 – 9 mm	4.0 - 6.0	5.0 - 7.5
CNS11– 11 mm	5.0 - 8.0	7.0 - 8.5

*See definitions in Figure 2

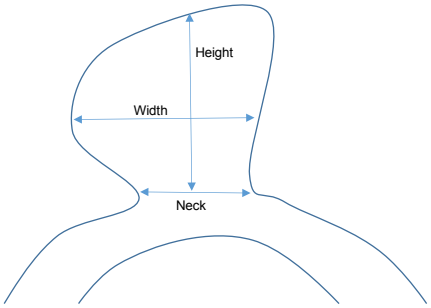

Figure 2. Aneurysm dimension definitions

7.6 Baseline

The baseline evaluation is performed after signing the consent form and prior to the study procedure. During the baseline evaluation, the investigator and/or coordinator will record basic medical information on the study case report form (CRF), including known diagnoses and daily medication use. Any relevant neurologic findings will be recorded on the CRF. An NIH Stroke Scale[1] score is to be recorded. NIH Stroke Scale is a commonly used assessment of clinical findings in patients with stroke. Since most unruptured IAs are asymptomatic, it is anticipated that most subjects will have a baseline NIH Stroke Scale score of 0. The investigator should have an up-to-date NIH Stroke Scale certification to complete the assessment. A modified Rankin Scale (mRS) will also be recorded at baseline. The mRS is a widely used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. Premenopausal females will undergo a pregnancy test. Relevant pre-procedure imaging should be submitted to the independent core laboratory.

7.6.1 Angiogram

The angiogram should be performed prior and separate from the Contour Neurovascular System™ implant placement procedure to allow proper assessment of the target IA being treated. The angiogram will include the acquisition of a 3D rotational angiogram of the aneurysm and parent vessel. It is not required to repeat the cerebral angiogram at baseline if the patient has had a cerebral angiogram that includes a 3D rotational angiogram within three (3) months of enrolment since the final determination of eligibility is based upon the cerebral angiogram at the time of the procedure.
All images obtained at baseline, including the 3D angiogram, are to be submitted for review to the Sponsor's representatives to confirm the subject's eligibility for use of the Contour Neurovascular System™. The Contour Neurovascular System™ procedure may be scheduled following confirmation from the Sponsor. Additionally, the images obtained at baseline will be submitted to the independent core laboratory.

7.7 Study Procedure

7.7.1 Preoperative Preparation

The subject undergoes standard preoperative preparation. The procedure must be performed under general anaesthesia.

7.7.2 Arterial Access

Standard methods are used to gain access to the femoral artery. Standard methods are used (e.g., sheaths and guide catheters) to obtain access to the IA. Tri-axial approach, although not mandatory, is highly recommended.

7.7.3 Angiogram

A cerebral angiogram of the target IA and the parent artery at the beginning of the procedure will be performed to confirm final eligibility for the study.

[1] Described at: http://www.ninds.nih.gov/doctors/nih_stroke_scale.pdf

7.7.4 Contour Neurovascular System™ Placement

Contour Neurovascular System™ placement is described in detail in the Instructions for Use. Briefly, the target IA is accessed via standard methods. A 0.027" microcatheter is placed into the target IA. The Contour Neurovascular System™ device is introduced into the microcatheter and slowly delivered into the target IA. Once the Contour implant is in the appropriate location, the device is detached via a standard electrolytic mechanism.

A final post-placement angiogram, which includes a 3D angiogram of the aneurysm and parent vessel, will be performed and all devices are removed from the body. All relevant radiographic images should be saved. Specifically, the investigator should document flow disruption compared to pre-placement flow. Any device deficiencies, technical complications or adverse events occurring during the procedure should be noted in the CRF.

All images captured during the procedure, including the 3D angiogram, are to be submitted to the independent core laboratory.

Peri-operative anti platelet use is not excluded and may be used at the discretion of the operator.

7.8 Hospital Discharge

The subject will be discharged from the hospital as per standard practices. Prior to discharge, the investigator should evaluate the subject for any adverse events and perform a neurologic examination.

7.9 Follow-Up

The subject will have a follow-up visit at six (6) weeks, six (6) months, and one (1), two (2), three (3), four (4) and five (5) years after the study procedure. At each study visit, the subject should be assessed for any new adverse events. A standard neurologic examination should be performed to evaluate for any new adverse events. A modified Rankin Scale (mRS) will be recorded at each follow-up visit. It is expected that most target IAs will be asymptomatic and the likelihood of post-placement neurologic changes is very low. The NIH Stroke Scale is recorded if a stroke has occurred.

Cerebral angiography will be repeated at six (6) months and one (1) year. At six (6) months, the cerebral angiography will include a 3D angiogram, and at one (1) year the angiogram will include the conventional AP, lateral and working projections. The investigator should ensure that follow-up angiography is done with identical views to maximize the ability to compare baseline and post-treatment views. All angiographic images should be submitted to the independent core laboratory. The target IA status will be evaluated by an independent core laboratory using an appropriate aneurysm scoring scale(s) such as the Raymond Scale and/ or the Web Occlusion Scale (WOS).

An MRI/MR angiogram (TOF & Contrast enhanced MRA) will be performed in all subjects at 6 months follow up. The purpose of the MR is to establish and compare the MR and angiographic appearances of the target IA.

If the cerebral angiogram shows complete occlusion at both the 6-month and 1-year time frames, the investigator may choose alternative methods for the 2, 3, 4 and 5-year angiography (e.g., MRI/MRA). If the cerebral angiogram at either 6 months or 1 year shows incomplete target IA occlusion, the 2, 3, 4 and 5-year exam should include a standard cerebral angiogram.

The subject's participation in the study is complete after the 5-year visit and angiogram/MR are completed.

The study's schedule of assessments and allowed post-treatment visit windows are shown in **Table 3** below.

Table 3. Schedule of assessments

	Baseline	Procedure	Discharge	1 month ± 2 weeks	6 month ± 1 month	Year 1 (± 1 month)	Year 2, 3, 4, 5 (± 1 month)
Medical history and medications	X						
Neurologic exam	X		X	X	X	X	X
NIH Stroke Scale	X		X*	X*	X*	X*	X*
Modified Rankin Scale (mRS)	X		X	X	X	X	X
Pregnancy test (pre-menopausal female)	X						
Cerebral angiogram	X** w/3D	X w/3D			X w/3D	X	X§
Adverse events		X	X	X	X	X	X
Procedure information		X					
Aneurysm scoring scale		X			X	X	X#
MRI/MRA					X		X§

*The NIH Stroke Scale score should be obtained within 7 days after stroke in the event a subject is diagnosed with a stroke

**Baseline cerebral angiogram with 3D can be completed within 3 months of enrolment

Aneurysm scoring scale completed when cerebral angiograms are performed

§MRA/Cerebral Angiogram Optional: If the cerebral angiogram shows complete occlusion at both the 6month and 1-year time frames, the investigator may choose alternative methods for the 2, 3, 4 and 5-year angiography (e.g., MRI/MRA).

7.10 Early Withdrawal

Reasons for subject withdrawal prior to study completion will be documented on the CRF. Valid reasons for early study withdrawal include:

- Death
- Adverse event or other medical condition that prevents study participation
- Withdrawal of voluntary consent
- Loss to follow-up

- Study is terminated

At least three documented attempts will be made to contact any subject who is lost to follow-up. If the study is terminated for any reason, the governing Ethics Committee will be notified.

7.11 Variables

7.11.1 Primary Variables

The primary varibles are safety as this is a pilot study.

The safety variables to be collected and reported are the occurrence and frequency of AEs, ADEs, SAEs, SADEs and USADEs.

Specific AEs associated with this procedure that shal be evaluated include but are not limited to: blood vessel perforation or rupture, unintended thrombosis, adverse tissue reaction, infection, and hematoma formation, and major ipsilateral stroke/ SAH or death due to neurologic cause within 6 months after treatment.

7.11.2 Secondary Variables

Secondary variables to be collected and reported in order to aid in the design of future studies are listed below.

Efficacy: Efficacy variables are related to the ability of the device to emobolize the aneurysm and shall be analyzed relative to the baseline visit. The variables to be collected and reported shall include but are not limited to:

Angiographic and/or MRI/ MRA assessment of aneurysm occlusion including evaluation of occlusion grade, parent vessel patency, physical positioning, occlusion durability, and any device migration.

7.11.3 Independent Analysis of Imaging

Follow-up imaging (i.e., cerebral angiograms and/or MRI/MRA) will be evaluated and angiographic assessments of the aneurysm will be completed by an independent core laboratory with experience in neurovascular imaging of IAs. Clinicians responsible for imaging analyses at the core laboratory will not have any financial conflict with the study sponsor and will not be affiliated with a clinical study site. An imaging guidance document will be prepared before analysis begins at the independent core laboratory.

8 Adverse Events

Definitions of adverse event subtypes are provided in Table 4 below. The occurrence of all adverse events will be reported by the clinical site investigator on a specific case report form (CRF).

NOTE: As detailed in section 8.3, the reporting of AEs shall follow MEDDEV 2.7/3, 2015 and shall not make any difference between anticipated and unanticipated AEs.

Table 4. Adverse event definitions per ISO 14155:2011

Adverse event	An Adverse Event (AE) is: "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices."
Adverse device effect	An Adverse Device Effect (ADE) is: "adverse event related to the use of an investigational medical device." Note 1: This definition includes events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious adverse event	A Serious Adverse Event (SAE) is: "an adverse event that • led to death, • led to serious deterioration in the health of the subject that either resulted in ○ a life-threatening illness or injury, or ○ a permanent impairment of a body structure or a body function, or ○ in-patient or prolongation hospitalization, or ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or body function, • led to foetal distress, foetal death, or a congenital abnormality, or birth defect." Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered to be a serious adverse event.
Serious adverse device effect	A Serious Adverse Device Effect (SADE) is: "adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event."
Unanticipated serious adverse device effect	An Unanticipated Serious Adverse Device Effect (USADE) is: "a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report." Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

8.1 Stroke

The risk of stroke after treatment with the study device is low. However, if stroke occurs, the subject should be appropriately treated according to institutional standards. The investigator should obtain an NIH Stroke Scale within 7 days after stroke and record the value in the CRF.

8.2 Independent Medical Monitor

An independent Medical Monitor will be appointed for the study who will be qualified by background and training and have expertise in neurovascular treatment of IAs. The independent Medical Monitor will review all adverse events to ensure they are reported accurately and in sufficient detail, and will make a final determination regarding relatedness to the investigational device and/or procedure. The Medical Monitor will not be an investigator on the study and will not be affiliated with a clinical site that is participating in the study.

8.3 Adverse Event Reporting/Analysis

In compliance with MEDDEV 2.7/3, 2015, for pre-market studies, the Sponsor is responsible for submitting reports to the Competent Authority as required by the applicable regulations and guidelines.

Specific requirements are as follows:

Table 5 Sponsor Adverse Event Reporting

Event	CA Reporting Timelines
SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it	Immediately, but not later than 2 calendar days after awareness by Sponsor of a new reportable event or of new information in relation with an already reported event, per MEDDEV 2.7/3
Any SAE	Immediately, but not later than 7 calendar days following the date of awareness by Sponsor, per MEDDEV 2.7/3
Any investigational device deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate	Same as above
New findings/updates in relation to already reported events	Same as above

The Investigative Site shall report all SAEs to the study sponsor or the sponsor's designee and independent Medical Monitor within 48 hours of occurrence.

9 Statistical Analysis

9.1 General Principles

This is a pilot study intended to collect and report data on the use of the Contour Neurovascular System™.

The primary analysis for all baseline characteristics and study variables will include all available data for all enrolled subjects. Standard summary statistics will be calculated for all study variables. For continuous variables, statistics will include means, standard deviations, medians and ranges. Categorical variables will be summarized in frequency distributions.

Statistical analyses will be conducted in SAS version 9.3 or above (SAS Institute, Cary, N.C.), R version 3.2 or above (R Core Team, http://www.R-project.org) or another validated statistical software package.

For adverse event reporting, the primary analysis will be based on subject counts, not event counts. Both subject counts and event counts will be presented in tabular summaries of results.

As this is a pilot study, formal hypothesis testing of the study variables will not be performed and multiple testing procedures are not incorporated in the statistical analysis.

9.2 Multi-centre Trial Considerations

A maximum of five (5) clinical sites will participate in the study. The maximum enrolment at any one site will be 20 subjects.

This is therefore a multi-centre clinical study with standardization of subject enrolment, data entry and adverse event reporting. All investigational sites will follow the requirements of a common protocol, data collection procedures and forms.

Data will be presented in summary form for all subjects enrolled. Given the intended sample size, formal tests of poolability are expected to have low power and will not prospectively be performed but primary variables will also be presented separately for each center.

9.3 Interim Analysis

No formal interim analyses are defined for purposes of early study termination.

9.4 Sample Size

As formal hypothesis testing is not a study objective, the sample size is based on precision of estimation.

A sample size of up to 45 subjects enrolled, with at least 30 subjects providing evaluable safety data, gives a standard error for the primary safety variable between 4.5% and 5.4%, which is sufficient for estimation of the safety incidence rate.

9.5 Number of Clinical Sites

A maximum of five (5) clinical sites will participate in the study. The maximum enrolment at any one site will be 20 subjects.

10 Additional Trial Characteristics

10.1 Measures Taken to Avoid Bias

Several measures have been included in the CIP in avoidance of bias, including the following:

1. The study has been designed to ensure treatment and follow-up of subjects are consistent with current medical practice.
2. The study will be approved by the central Ethics Committees (ECs) prior to initiation and will undergo continuing review by the ECs as the study progresses. Additionally, each clinical site will provide further oversight and approval of the study.
3. All investigators must disclose potential conflicts of interest, including financial interests, to the study sponsor prior to participation in the study.
4. Data from all investigative sites will be monitored throughout the study.
5. An independent Medical Monitor will adjudicate adverse events that may be considered serious and/or device related.
6. Imaging obtained during the procedure and follow-up period will be reviewed by an independent Core Laboratory to verify the status of the Contour implant and the surrounding vasculature.

10.2 Special Equipment for Investigation

Apart from the study device, all equipment used in the trial will be maintained and calibrated in accordance with the clinical site institution's policies and procedures and will be reviewed as part of routine monitoring visits.

10.3 Procedure for Replacing Withdrawn Subjects

Subjects who withdraw from the study will not be replaced.

10.4 Subject Pregnancy

The exclusion criterion specifies that those patients who are pregnant, breastfeeding or planning pregnancy in the next two years be excluded from the study. Should a subject become pregnant after enrolment in the study, the subject will continue to be seen by the investigator at the time points defined in the CIP to ensure proper follow-up of the subject. The subject will be assessed for any new adverse events, undergo a standard neurologic examination, a modified Rankin Scale (mRS) score will be recorded and a NIH Stroke Scale will be recorded if a stroke has occurred. It is expected that the cerebral angiogram required at a specific follow-up visit will not be completed if the subject is pregnant or breastfeeding. Additionally, if a subject is pregnant or breastfeeding, any other imaging specified by the CIP for a specific follow-up visit will only be completed with the concurrence of the subject's obstetrician/pertinent clinician.

10.5 Investigational Device(s) and Comparator(s)

The investigational device is the Contour Neurovascular System™. No comparator devices will be used in the study.

10.6 Justification for Comparator

This study has no concurrent comparator.as this is a pilot study.

10.7 Other Devices Used During Study

Several devices are standardly used during endovascular procedures to treat IAs. Other than the investigational implant and implant delivery system, no special devices are required for this study.

10.8 Investigational Devices

A single investigational device is expected to be used for each target IA. In some situations, an investigational device might be inserted into the body but removed prior to deployment, in which case another device package could be opened and used.

Device accountability records should be maintained at each study site. The quantity of devices received by the study site, those returned to the sponsor (if applicable), and those devices used at the clinical site will be recorded in the device accountability record. The investigator must explain in writing the reasons for any discrepancy noted in device accountability. Device accountability will be verified during routine monitoring visits at the clinical sites.

10.9 Total Expected Trial Duration

Enrolment is expected to be complete in 6 months. The investigation is expected to last at least 5 ½ years, including enrolment.

11 Study Management

This study will be run according to ISO 14155:2011, the Declaration of Helsinki, conditions imposed by local ethics committees (ECs), and any applicable regulatory requirements. For this study, the sponsor will have certain direct responsibilities and may delegate other responsibilities to appropriate consultants and/or contract research organizations (CROs). Together, the sponsor and all related participants will ensure that the study is conducted according to the above standards and all applicable regulations. All personnel to participate in the conduct of this clinical trial will be qualified by training, education and/or experience to perform his or her respective tasks.

11.1 Investigator Responsibilities

This section highlights responsibilities of the principal investigator (PI) at each site regarding this investigation. The PI, i.e., the main investigator at each study site, is responsible for managing day-today aspects of the study. The PI will take steps to ensure compliance with the CIP and associated documents and processes. The PI also protects data integrity and the rights, safety and well-being of clinical study subjects.

11.1.1 Disclosure

All investigators must disclose potential conflicts of interest, including financial interests, to the study sponsor, both before and during conduct of the clinical study as well as up to 1 year after the study has completed.

11.1.2 Additional Site Team Members

The site may add new members to the investigational team. Training of new personnel will be documented before new personnel participate in the study. New investigators should disclose potential conflicts, as described in **Section 11.1.1**.

11.1.3 Communications with EC

The site Principal Investigator (PI) and the site clinical study team are responsible for communication with site ethics committee. The Sponsor and/or designee is responsible for communication with central ethics committees. The PI will:

- provide the sponsor with copies of any relevant EC communications regarding this CIP
- comply with requirements from the EC regarding the CIP
- obtain written/dated approval/favourable opinion from the site EC, before starting the study or recruiting subjects
- obtain written/dated approval from the site EC before implementing any changes in a CIP amendment
- ensure the timeliness of safety reporting to the site EC
- promptly report deviations from the CIP to the EC that affect the rights, safety or well-being of the subject or the scientific integrity of the CIP
- keep all EC communications in its study file

11.1.4 Informed Consent

The PI is responsible for the informed consent (IC) process in this CIP. The PI will ensure that:

- the IC used for the consent process is the most current IC, has been approved by the EC and is consistent with any requirements imposed by the EC
- the IC process occurs consistent with ISO 14155, and importantly, prior to any procedure specific to the clinical investigation is applied to the subject.
- a copy of the signed/dated IC form is kept in the subject's records, and
- either he/she or an authorized designee conducts the consent process consistent with ISO 14155

11.1.5 Subject Identification Log

The PI or designee will maintain a log of all subjects enrolled in the study. The log links study identification (ID) numbers to identifying patient information (name, contact information). The log will be housed securely.

11.1.6 Compliance with CIP

The PI is responsible for ensuring that his/her site complies with the CIP. The PI will:

- maintain oversight of the study at the clinical site
- sign an investigator agreement form
- conduct the investigation in compliance with this CIP, applicable sections of ISO 14155, and requirements of the EC to ensure the safety and well- being of study subjects
- create, maintain and make available source documents for study subjects
- not implement any change to the CIP without prior approval from the sponsor, local EC, and (if required) regulatory bodies
- document all deviations from the CIP[2]
- ensure proper use and accountability of investigational devices
- ensure that the site has adequate staff and capabilities
- ensure that site equipment used in the study is maintained and calibrated

[2] The sponsor may also document deviations from the CIP.

- ensure the accuracy, completeness and timeliness of study data in CRFs and reports
- allow and support sponsor monitoring and auditing activities
- be available to monitors and the sponsor to address questions during study visits
- be available and support regulatory authorities during audits
- respond in a timely manner to sponsor inquiries
- make reasonable efforts to prevent early withdrawal
- make reasonable efforts to ascertain the reason for early withdrawal

11.1.7 Subject Records

The Investigator will maintain original source documents from which study-related data are derived, which include, but are not limited to:

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

11.1.8 Subject Accountability

The PI will make reasonable efforts to account for all study subjects, especially those who withdrew. If withdrawal is due to problems with study device safety or performance, the PI will obtain the subject's permission to follow his/her status/condition outside the clinical investigation, if possible.

11.1.9 Device Deficiencies and Malfunctions

Throughout the study, the PI or designee and sponsor will report and document all device deficiencies and malfunctions related to the identity, quality, durability, reliability, safety or performance of the device. This includes reporting of device deficiencies/malfunctions that did not lead to an AE but could have if: 1) suitable action had not been taken, 2) intervention had not been made, or 3) circumstances had been less fortunate.

The PI should make every effort to return devices suspected of deficiency or malfunction to the sponsor for analysis.

11.1.10 Medical Care

The PI will provide standard medical care to study subjects, including:

- informing the subject of the nature and possible cause of any AEs experienced
- informing the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required

- providing the subject with medical care required for possible emergency situations related to the clinical investigation
- ensuring that clinical records are clearly marked to indicate that the subject is enrolled in this study
- providing, if required, the subject with documentation that the subject is enrolled in this study
- informing the subject's personal physician about the subject's participation in the study **11.1.11**

Safety Reporting

The PI will make reasonable and consistent efforts to document all adverse events (AEs). The PI will:

- record every AE and observed device deficiency or malfunction
- report all SAEs and device deficiencies to the sponsor within 48 hours of occurrence
- provide sponsor-requested details for AEs and device deficiencies/malfunctions in a timely manner
- report SAEs to the EC and/or regulatory authorities consistent with local or national requirements

11.1.12 Device Accountability

Device accountability records must be maintained at the study site. All investigational devices will be traced by part number, lot number, and if applicable, serial number. The investigator is responsible for accounting for all devices transferred to his position. The investigator will ensure that any devices stored at the site are in a secure location.

The sponsor will ensure that investigational devices are tracked carefully from the time of provision to the site to disposition.

11.1.13 Recording Data on CRFs

The study will use case report forms that have been standardized for the study to collect data. Site personnel will be trained in use of the CRFs before study initiation. The PI will ensure that data recorded in CRFs in a timely manner and are accurate, consistent with source documents, reliable and logically correct. The investigator must explain in writing the reasons for any discrepancy noted in device accountability.

The PI or designee will review, sign and date all completed CRFs. After entry into the electronic database and monitoring has occurred, the clinician will review, sign and date verification of data entry.

11.1.14 Investigator Reports

The investigator must report particular items related to the study according to **Table** . At the investigator's discretion, the sponsor may help to prepare reports.

Table 6. Reporting activities

Report	Submit To	Description / Constraints

SAE & Unanticipated Adverse Device Effect	Monitor & EC	If an unforeseen complication is determined to be an unanticipated adverse device effect, then the investigator's report must be submitted within 48 hours after the investigator first learns of the effect.
Withdrawal of EC Approval	Sponsor	The investigator must report a withdrawal of the reviewing EC approval within 5 working days.
Progress Report	EC	The investigator must submit this report if the study lasts longer than one year.
Deviation from Investigational Plan	Sponsor & EC	If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be preapproved by the Sponsor, reviewing EC, and the Competent Authorities if applicable. If the deviation does not affect these issues (study soundness, rights, safety, etc.) then only the Sponsor must preapprove it.
Failure to Obtain Informed Consent	Sponsor & EC	The Investigator must make notification within 5 working days after device use. The report must include a brief description of the circumstances justifying the failure to obtain informed consent and include written concurrence by a licensed physician/clinician not involved in the investigation.
Final Report	Sponsor & EC	This report must be submitted within three months after termination or completion of the investigation.

11.1.15 Final Report

The sponsor and coordinating investigator will prepare a final report when the study is completed or if it is terminated. The PI will provide the report to the EC and regulatory authorities as required.

11.1.16 Document Retention

The PI will maintain documents related to this investigation until 2 years after the study is complete. Some EU countries may require longer document retention periods. The PI may transfer custody of records to another person/party and document the transfer at the clinical site with notification to the sponsor or at the sponsor's facility. The PI and/or site personnel cannot destroy the study documents without first obtaining written approval from the sponsor. Required documents to retain are extensive and are listed in Annex E of ISO 14155:2011(E).

11.1.17 Source Documents

The PI will retain original source documents (or copies thereof) used to verify study data. The PI or site personnel will provide written confirmation with signature and date that copies of source documents are true reproductions of the original source document. The sponsor may have access to original source documents upon request.

11.2 Sponsor Responsibilities

11.2.1 Overall Conduct of Study

Cerus Endovascular Ltd, the study sponsor, is responsible for the overall conduct of this investigation, including:

- implementing written clinical quality procedures to ensure that the clinical investigation is designed, conducted and monitored, and that data are generated, documented, recorded and reported in compliance with Good Clinical Practice (GCP), the CIP and its amendments, and any other applicable standards and regulatory requirements
- maintaining records to document the compliance of all parties involved in the clinical investigation
- documenting significant/key correspondence with all parties involved in the clinical investigation
- ensuring that the clinical investigation is appropriately monitored by determining the extent and nature of monitoring
- reviewing monitoring reports and following up any required actions in those reports
- taking prompt action to secure compliance with all clinical investigation requirements
- submitting progress reports, including safety summary and deviations, when requested, to all reviewing ECs and the regulatory authorities

11.2.2 Clinical Personnel

The sponsor will designate or appoint one or more study monitors and will ensure documentation of training of monitors sufficient to conduct the investigation.

11.2.3 Study Preparation

Before starting the study, the sponsor will:

- define all roles and responsibilities related to this investigation
- ensure that all required signatures are obtained
- ensure the accuracy of translation, if required, of any aspect of the study prior to initiating the study at the selected site
- develop a complete set of documents necessary to begin the study, including consent forms, case report forms (CRFs) and, if required, an investigator's brochure
- document any financial arrangements between the PI or investigation site and the sponsor
- submit any required application(s) to begin the investigation to appropriate regulatory authorities for review, acceptance or permission, as required
- ensure documented EC approval before the study is started
- ensure documented ongoing EC approval of the study
- ensure that the site's ICF is consistent with requirements of ISO 14155:2011
- ensure that any modifications required by the EC or regulatory authority are made and documented by the PI

11.2.4 Investigational Site Qualification

The sponsor will ensure that each investigational site:

- has a qualified PI

- has adequate staff, resources, including facilities, laboratories, equipment and a qualified investigation site team
- is able to handle all potential adverse effects has access to an adequate number of subjects on a timely basis

Site qualification will be documented.

11.2.5 Investigational Site Initiation

The sponsor will ensure that the site does not begin the study until all of the following have been collected or performed and documented:

- training in requirements and contents of this CIP and its associated documents (e.g., CRFs, IFU, IB, etc.)
- written EC approval, including EC-approved IC form
- list of EC members or EC assurance number
- documentation of investigational team's designated roles and responsibilities
- documentation of investigator conflict of interest
- signed investigator agreement
- signed clinical trial agreement (CTA). The CTA is the legal agreement between the site, PI and sponsor that covers all activities related to the study. The agreement will indicate that, by participating in a clinical investigation, the parties may share some regulatory responsibilities with the sponsor.
- current curriculum vitae of PI and any sub-investigators

11.2.6 Monitoring

The sponsor is responsible for study monitoring. Monitoring is done to verify that the study has been performed consistent with this CIP (and its amendments), and any other local or national requirements. The sponsor will document a monitoring plan.

11.2.7 Qualified Monitors

The sponsor will ensure that study monitors:

- understand requirements of this CIP
- are knowledgeable on the use of the study device
- are knowledgeable on the informed consent process
- are trained on the applicable portion of the sponsor's quality control system
- are trained in any special procedures required for monitoring this CIP Training will be

documented in the sponsor's files.

11.2.8 Remote Monitoring

Data collected during the study will be systematically reviewed by the sponsor to identify inconsistencies, potential data errors or potentially unclear information. Statistical techniques may be used to identify outliers. Queries will be sent to the site for data that may represent errors or that require clarification.

11.2.9 On-Site Monitoring

The monitor will perform on-site monitoring visits to verify:

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- compliance with this CIP and its amendments
- compliance with requirements, if any, of the governing /EC
- compliance with local regulations pertaining to a clinical study
- compliance with requirements, if any, of regulatory authorities
  continued adequacy of investigation site resources, including laboratories, equipment and the investigation site team
- continued access to a sufficient number of potential study subjects
- compliance with the informed consent process
- all CIP requirements are met before the study begins at the site
- adequate storage, maintenance and accountability of investigational devices
- adequate storage and maintenance of source documents and other related records
- source documents are accurate, complete and up-to-date
- CRFs and queries are completed adequately, in a timely manner, and consistent with source documents
- all AEs, deviations and device deficiencies are documented and reported to the sponsor
- any device deficiencies/malfunctions that could have led to an SAE are reported to the sponsor without unjustified delay
- all SAEs are reported to the EC, if required
- maintenance of required reports, notifications, applications, submissions and correspondence in the PI's files
- maintenance and calibration (and documentation thereof) of all equipment relevant to this CIP
- maintenance and documentation of current laboratory normal values and certifications, if required
- subject withdrawal and reasons for withdrawal have been documented
- subject non-compliance with the requirements stated in the informed consent has been documented
- any corrective and preventive actions, as needed, have been implemented and are effective

The monitor will document site monitoring visits in a report that includes the site's compliance with the CIP. The report will include:

- date of monitoring
- site identification
- name of monitor and PI
- summary of what was reviewed
- summary of observations and findings
- summary of recommendations

The monitor will share all findings with the PI and the sponsor.

11.2.10 Close-Out

When the investigation is complete, the sponsor will ensure that sites undergo closeout activities, to include:

- all essential documents are available and present in the PI's files
- all CRFs are completed
- all queries are resolved

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- the status of all ongoing AEs is documented
- arrangements for record retention have been made
- all documents needed for sponsor's files are retrieved
- unused study devices are accounted for and returned to the sponsor
- local EC and regulatory authorities are notified, if applicable In addition, the sponsor will:

provide a clinical investigation report to sites

- ensure that clinical investigational report is provided to EC, investigators and regulatory authorities (if required)

11.2.11 Auditing

At the discretion of the sponsor, any site may undergo audit by the sponsor or a sponsor-designated third party. Audits evaluate compliance with this CIP, ISO standards or other regulatory requirements.

11.2.12 Safety Reporting

The sponsor is responsible for ongoing safety evaluation in this CIP. Sponsor activities regarding safety include:

- ensuring the independent Medical Monitor reviews all adverse events to ensure they are reported accurately and in sufficient detail,
- classification of all AEs
- review of all AEs reported in the study
- confirm site's classification of AEs in terms of severity and relatedness to the study device
- review of device deficiencies and malfunctions, including determination and documentation of whether deficiencies/malfunctions could have led to an SAE
- ensuring the reporting of all SAEs and device deficiencies/malfunctions that could have led to an SAE to the EC and, if required, regulatory authorities in a timely fashion
- informing all site PIs in writing of all SAEs at all sites in a timely fashion
- ensuring that the EC and the regulatory authorities are informed of significant new information about the clinical investigation
- updating the risk analysis and assessment of corrective or preventive actions potentially required as a result of new information obtained in the investigation

The sponsor will evaluate all serious adverse events. The sponsor will investigate each SAE to determine whether the event represents an unanticipated serious adverse device effect (USADE). The sponsor will report any event to regulatory authorities, investigators and reviewing ECs as necessary. If an investigation shows that a USADE presents an unreasonable risk to subjects, the sponsor will terminate all investigations or parts of investigations presenting that risk as soon as possible. The sponsor will only resume a terminated investigation after corrective actions have taken place, site investigators are informed and ECs have been notified and given approval to resume the study.

11.2.13 Device Deficiencies and Malfunctions

A device deficiency is defined as inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling (ISO 14155:2011). A device malfunction is a failure of a medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or CIP (ISO 14155:2011).

The sponsor will conduct an analysis of any device deemed deficient or malfunctioning by the site and track underlying causes for failure.

All deficiencies and malfunctions will be evaluated against applicable requirements for reporting.

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11.2.14 Suspension or Termination of Study

The sponsor may temporarily suspend or terminate the study at any time at one or more sites for the following reasons:

Suspicion of risk to patients, including occurrence of high rate of known AEs or unexpectedly high rate of unexpected AEs

- Poor site compliance with this CIP
- Inadequate site enrolment
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Persistent non-compliance with EC or regulatory requirements
- Persistent failure to comply with obligations arising from the clinical trial agreement • Other business reasons (e.g., insolvencies or business entity liquidation)

The sponsor will document reasons for study suspension and notify relevant site PIs and the coordinating investigator. The sponsor will ensure that the EC and regulatory authorities (if required) are notified in a timely manner. If suspension occurred because of a safety issue, all site PIs will be notified. When terminating the study, the sponsor and investigator will assure that adequate consideration is given to the protection of the subjects' interests.

11.2.15 Resuming a Temporarily Suspended Study

If the sponsor temporarily suspends the study and wishes to resume it, the sponsor will inform the coordinating investigator and site PIs, ECs and (if appropriate) regulatory authorities. The sponsor will provide a rationale for resuming the study. ECs must provide written approval before the study is resumed at the site.

11.2.16 Suspension of Study Centre

The Sponsor may discontinue a study centre if the centre fails to recruit sufficient patients or if the centre is found to be in recurrent or continuous non-compliance with the Clinical Investigation Plan and/or ISO 14155:2011 or other applicable requirements.

11.2.17 Document Control

The CIP may require updating during the study. Important sponsor documents related to this CIP will be controlled with version numbers to ensure traceability. Expired versions of documents will be archived by the study sponsor.

The sponsor will ensure that amended documents (e.g., new versions) are, where required, approved by the EC before they are used in the study. Reasons for amendment will be justified and documented. The sponsor will ensure that the PI has acknowledged receipt of significant new documents.

11.2.18 Clinical Investigation Report

The sponsor will be responsible for ensuring that a clinical investigation report is prepared which summarizes study findings. The report will be prepared even if the investigation is terminated early.

The report will:

- be in written form
- be completed even if the study is premature terminated

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- will include device identification and description
- summarize clinical trial methodology
- include a summary of deviations
- provide adequate analysis with statistical analysis, where appropriate,
- critically appraise the aims of the study and whether the aims were met not provide personally identifying subject information
  be made available to the study Principal Investigator prior to finalization for comment and review
- signed by the study Principal Investigator
- provided to ECs and regulatory authorities, as per applicable requirements

The sponsor is committed to publication and dissemination of the results of this study. At the conclusion of the study, a multi-centre publication will be prepared suitable for submission in peer-reviewed medical literature. The publication of results from any single centre experience within the trial is not allowed until the aggregate study results have been published, unless there is written consent from the study sponsor.

11.2.19 Document Retention

The sponsor will maintain documents related to this investigation as required by applicable regulatory standards. Required documents to retain are extensive and are listed in Annex E of ISO 14155:2011

REVISION HISTORY

Rev	DCO	Change Description	Release Date
A	0068	Initial release.	2016-05-17
B	0081	Add -01 to document number for clarity Add Revision History	03 Jun 2016
C	0101	Add Discharge to Modified rankin Scale (mRS) in Table 3 in section 7.9 Update sections 9.1 and 9.2	26 Jul 2016
D	0108	Changed title to Pilot Study. Updated primary and secondary Objectives. Changed Endpoints to Variables and updated. Changed Effectiveness to Efficacy. Updated safety variables. Update Table 2. Update Section 8. Updated Table. 6.	05 Aug 2016
D	0158	Correction Only – Correct Revision from C to D on pages 2- 32 and correct DCO # 109 to 108. Move Revision History table to end of document	28 Nov 2016
E	0275	Addition of CE Mark language (pg 4); removal of requirement for minimum height (pg 10, 11); Clarification of MRI/MRA and cerebral angiogram at years 2, 3, 4, 5 (pg. 14)	28 Aug 2017

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F	0323	Change Lead Principal Investigator (page 2) Removal of CE Mark language (page 4); Update Device Manufacturing Overview (page 8)	14 Nov 2017

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APPENDIX A – Statement of Compliance and Signature

Clinical Investigation Number: DNX065

The signature below signifies that I have read this Clinical Investigation Plan and agree to adhe
requirements. I will provide copies of this Clinical Investigation Plan and all pertinent informat
personnel under my supervision. I will discuss this material with them and ensure they are fully
regarding the Plan's requirements. I will ensure that the study is conducted in compliance with
14155:2011, the Declaration of Helsinki, and the pertinent individual country laws/regulations
regulatory requirements including requirements imposed by Ethics Committee (EC).

Site Name: LEEDS TEACHING HOSPITAL GENERAL INFIRMARY

Site Principal Investigator: DR. TUFAIL PATANKAR
Print Name

Signed: [signature]

Date: 6/9/19.