# Contour Neurovascular System™
# European Pre-Market Unruptured Aneurysm Study (CERUS)
# February 5, 2019
# NCT Number 03680742


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# Study Information

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| **Protocol Name** | **Contour Neurovascular System™ European Pre-Market Unruptured Aneurysm Study (CERUS)** |
| **Protocol Number** | **DNX099-01** |
| **Device Name** | **Contour Neurovascular System™** |
| **Manufacturer** | **Cerus Endovascular, Inc.**<br>47757 Fremont Blvd<br>Fremont, CA 94538<br>United States |
| **Core Lab** | **Eppdata GmbH**<br>Lokstedter Steindamm 18<br>22391 Hamburg, Germany |
| **Web-Based Image System** | **CIMAR**<br>Cimar UK Ltd<br>Kemp House 152-160 City Road London EC1V 2NX Telephone 0800 0930913 Email info@cimar.co.uk |
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List of principal investigators and investigation sites will be maintained separately and is available upon request.

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# 1 Overview

This document provides a detailed plan for the Contour Neurovascular System™ European Pre-Market Unruptured Aneurysm Study (CERUS).

# 2 Clinical Study Synopsis

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| **Study Title** | **Contour Neurovascular System™ European Pre-Market Unruptured Aneurysm Study (CERUS)** |
| **Study Purpose** | Cerus Endovascular, Ltd., is sponsoring a prospective, multi-center trial to document the safety and performance of the Contour Neurovascular System™ ("Contour").<br>The purpose of the study is to document safety and performance of the Contour in treatment for patients with intracranial aneurysms (IA). The data from the study will be reported as a Pre-Market study to the Notified Body to support CE Mark approval. |
| **Indications for Use and Intended Use** | The Contour is intended for the endovascular embolization of intracranial aneurysms. The device should only be used by physicians licensed and credentialed to perform endovascular embolization catheterization procedures. Physicians must be thoroughly familiar and experienced with standard vascular embolization techniques and trained on the Contour Neurovascular System™ before using the device. |

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| **Contour Training** | Cerus Endovascular will provide training using flow models, didactic slide presentation and implant simulation using a vascular simulation 3-D replicator. Physician proctoring will occur for the first three implants and a patient selection committee will provide guidance over the identification of all the study patient aneurysms at each site to facilitate successful patient identification and implantation. A web-based image system called CIMAR will be used to view and store angiographic images of patient aneuryms. |
| **Study Design** | Prospective, single arm, multi-center study. |

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| **Study Size and Duration** | **Study Size**: The study population will include 30 subjects enrolled and implanted at up to 10 centers in Europe.<br><br>**Study Duration**: It is expected that the study will take 9 months to enroll 30 patients. Follow-up for the primary endpoint is the 6-month visit. Total duration of enrollment (9 months), follow-up duration for primary endpoint (6 months), 12 months follow up and reporting (3 months) will take approximately 24 months.<br><br>Any patient for whom a failed implant attempt is performed will be followed for 1 month, or until resolution of any potential device or implanted related adverse events, whichever occurs last.<br><br>Any patient who is consented but has no implant attempt will be study exited. |

**Device Description**

The Contour device works by providing a physical barrier between the parent vessel and the intracranial aneurysm neck (as demonstrated by the Contour clinical investigations as well as the pre-clinical research) thereby excluding the aneurysm from the parent artery blood flow. The Contour implant is sized to provide a proper fit and position across the neck of the aneurysm. Therefore, blood flow is diverted away from entering at the neck, leading to reduction in flow into the aneurysm cavity with subsequent stasis followed by the formation of thrombus within the confines of the aneurysm. As wound healing progresses and fibrosis occurs over the ensuing days and months, it serves to strengthen the physical barrier between the parent vessel and the aneurysm cavity. The weakened vascular tissue of the aneurysm cavity, in particular the dome, is thus protected from the shear wall stresses generated by the previous blood flow.

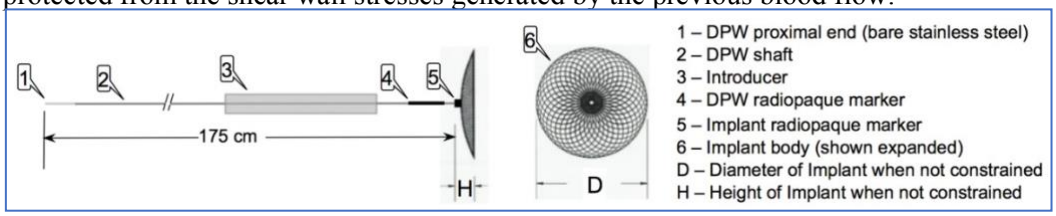



Figure 1 - Contour Neurovascular System™

The Contour Neurovascular System™ (CNS) (CNS05, CNS07, CNS09, CNS11) is an intrasaccular, self-expanding, embolization device intended for the treatment of unruptured intracranial aneurysms. The CNS is shown in Figure 1 and comprises an:

**Implant**

The implant is a self-expanding concave shaped device comprised of a double layer nickel-titanium and platinum wire mesh, and a platinum marker. The implant is packaged unconstrained in a protective dispenser hoop with an Introducer preloaded onto the DPW shaft just proximal to the implant.

**Detachable Pusher Wire (DPW)**

The DPW functions as a guidewire for implant delivery. The pre-attached DPW has a composite stainless steel and polymer construction, and a platinum marker. The DPW has a white fluorosaver mark on its proximal shaft that provides a visual indication of when the implant is approaching, but not exiting the distal end of the micro-catheter (MC).

**Introducer**

The Introducer is a single lumen polymer tube that is used to constrain the implant during introduction into the micro-catheter hub. The implant body and proximal marker can be visualized under fluoroscopy.

All devices are provided sterile and nonpyrogenic and are for single patient use only. The device is not an active device and does not incorporate any software/firmware.

The Contour Neurovascular System™ is offered in four sizes, suitable for embolization of intracranial aneurysm. Table 1 details the selection guideline for these four sizes:

The Contour Neurovascular System should only be used by operators who have received appropriate training in neurointerventional techniques. The operator delivers the implant to the aneurysm under fluoroscopic guidance using standard endovascular techniques and a commercially available 0.027" inner diameter MC[1]. The implant is electrolytically detached from the DPW using a commercially available detachable coil power supply[2,3].

Due to its unique placement across the neck of the aneurysm, the device acts as both a flow disrupter and diverter. The Contour only requires the neck and equatorial diameter to be taken into consideration when sizing the implant to the aneurysm (please see figure below). The height is not a requirement as the dome of the aneurysm is not required to stabilize the device. The device mesh provides a uniform scaffold distributed across the neck of the aneurysm for the establishment of neointimal development and unlike devices placed in the parent vessel, is not dependent on the use of dual antiplatelet therapy.

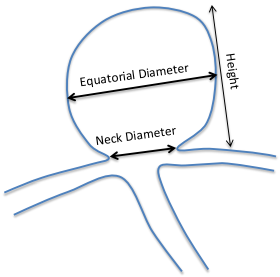
Table 1 - Implant Size Selection Guide

| REF (Catalog 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 |

[1] Stryker Neurovascular Excelsior® XT-27® (0.027" ID, 2.9F/2.7F OD, 150cm Length)

[2] Detachable Coil Power Supply: Stryker Neurovascular InZone® Detachment System, REF M00345100940

[3] Power Supply Detachment Cable: Stryker Neurovascular IZDS Connecting Cable, REF 00345110250


Equatorial Diameter
Height
Neck Diameter

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| **Objective and Endpoints** | The primary objective of this study is to document the safety and performance of the Contour Neurovascular System. The data from the study will be reported as a Pre-Market study to the Notified Body to support CE Mark approval. In addition, the data may be used to support US approval by the Food and Drug Administration (FDA) to market the Contour device in the United States.<br>**1. Primary Safety Endpoint:**<br>The proportion of subjects with death of any non-accidental cause or any major disabling stroke within the first 30 days after treatment or major disabling stroke or death due to neurological cause from day 31 to 6 months after treatment.<br>Note: Major Disabling Stroke is defined as an episode of neurological signs or symptoms that persist beyond 24 hours accompanied with evidence of ischemia/infarction on imaging that results in an increase of NIHSS from baseline by ³ 4 points and/or an increase from mRS baseline by >2.<br>**2. Primary Performance Endpoint:**<br>To demonstrate the occlusion rate on the 6 month angiogram as adjudicated by a core laboratory. Success will be defined as complete occlusion demonstrated by a Grade 1 using the Raymond Roy Scale. |

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| **Secondary Measures** | Additional measures will be summarized:<br>**Secondary Safety**:<br>• Serious Adverse Events (SAE) associated with the procedure or device<br>• All serious neurological adverse events **Secondary Performance**:<br>• Detailed assessment of aneurysm occlusion from post procedure to 6-months provided by the core lab review of the angiogram (DSA) including the following:<br>- Raymond Roy scale<br>- Modified Web Occlusion Scale<br>- Percent Occlusion<br>- Device Stability<br>• Rate of retreatment<br>• Summary of device performance including the following:<br>- Time required for implantation of the Contour<br>- Device sizes used<br>- Number of attempts to deploy the device<br>- Number of failed implant attempts<br>- Any reports of device deficiencies |
| **Sample Size** | A maximum of 35 subjects will be enrolled to obtain follow-up data for the primary analysis for 30 subjects while allowing for attrition to be submitted for CE Mark application. |

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| **Number of Sites** | A maximum of 10 European investigational sites will participate. |
| **Study Visits** | Baseline, procedure, discharge, one (1) month, six (6) months and twelve (12) months. |

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| **Enrollment and Eligibility** | **Enrollment**<br>To participate, patients must meet all inclusion criteria and no exclusion criteria listed below.All patients must sign a study-specific 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 at the time of consent and is considered a study subject in the reporting analysis group only when the patient is fully qualified and at least one Contour device has been placed into the patient's body. The following listing provides examples of patient enrollment scenarios for the study:<br>• The patient is not considered enrolled but not included in the primary analysis group in the study: if at the onset of the procedure in the initial DSA, the investigator determines the patient's IA was not suitable for treatment with the device, thus, no attempt was made by the investigator to place the device. The patient will be treated outside of the study per the investigator's usual practices. The reason for not treating the patient must be documented on a study exit form. The patient is not included in the primary analysis group because the Contour was never opened or deployed inside the patient. All patients will be listed in the final report.<br>• The patient is considered enrolled but not included in the primary analysis group in the study: at the onset of the procedure, the investigator determines the subject's IA was suitable for treatment with the device. The investigator attempted but was unable to place the 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 1 month visit. All failed implant attempts will be reported in the final report.<br>• The patient is considered enrolled and included in the primary analysis group in the study: if at the onset of the procedure, the investigator determines the subject's IA was suitable for treatment with the device. The investigator successfully placed the 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.<br>• The patient is considered enrolled and included in the primary analysis group in the study: if at the onset of the procedure, the investigator determines the subject's IA was suitable for treatment with the device. The investigator successfully placed the 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. |

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| **Eligibility Criteria** | Patients of all genders who meet all indications and contraindications will proceed to implantation.<br>**Inclusion criteria**<br>1. Patient's indication for treatment of unruptured aneurysm is according to the national/international guidelines.<br>2. Age 18-80 years at screening<br>3. Patients who are suitable for non-emergency endovascular embolization of saccular IAs<br>4. IA located at a bifurcation in the anterior or posterior circulation with dimensions consistent with implant size selection guidelines included in the IFU<br>5. 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<br>6. Patient able to able to give their informed consent can be included in this study. This must be demonstrated by means of a personally signed and dated informed consent document indicating that the subject has been informed of and understood all pertinent aspects of the study.<br>**Exclusion criteria**<br>The presence of condition that may create unacceptable risk during the aneurysm embolization procedure, such as patients with:<br>1. Ruptured aneurysm<br>2. Patient anatomy or physiology considered unsuitable for endovascular treatment<br>3. Contraindication for arterial access<br>4. Largest measured IA equatorial diameter >8.5 mm or <2 mm<br>5. Largest measured IA neck diameter >8 mm or <2 mm<br>6. Target IA contains other devices/implants (e.g., coils)<br>7. Known allergy to platinum, nickel or titanium<br>8. Known allergy to contrast agents<br>9. Contraindication to anticoagulants or platelet inhibitor medication<br>10. Stenosis of the target IA's parent vessel >50%<br>11. Anticoagulation medications such as warfarin that cannot be discontinued<br>12. Pregnant, breastfeeding or planning pregnancy in the next 2 years<br>13. Acute / chronic renal failure (including dialysis); Creatinine > 2.00 mg/dl or > 182 µmol/L<br>14. Myocardial Infarction, Stroke or TIA within the last 6 months<br>15. Any other medical issue within the brain that precludes the device implantation such as brain surgery, radiation in the target area of intervention, acute traumatic craniocerebral injury, etc.<br>16. Other medical conditions that cause an inability to comply with study requirements and/or that could increase the risk of neurovascular procedures or death within 2 years (e.g., liver failure, cancer, heart failure, chronic obstructive pulmonary disease, immunosuppression, neural disease, and hematologic disorders etc.) |

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| | 17. Participating in another study with investigational devices or drugs that would confound the effects of the study outcomes |

**Follow-Up and Required Assessments**

All implanted subjects will complete the scheduled follow-up assessments. Adverse events will be collected from device implantation through study duration. Table *2* highlights the required assessments:

Table 2. Schedule of Assessments

| | Baseline# | Procedure | Discharge | 1-month (30 days) | 6 months (180 days) | 12 months (360 days) |
|---|---|---|---|---|---|---|
| Medical history and medications | X | | | | | X |
| Neurologic Exam | X | | X | X | X | X |
| NIH Stroke Scale | X | X* | X* | X* | X* | X |
| Modified Rankin Scale (mRS) | X | | X** | X** | X** | X |
| Pregnancy test (pre-menopausal female) | X | | | | | |
| CT angiography (CTA) ^ | X# | | | | | |
| Magnetic Resonance Angiogram (MRA) ^ | X# | | | | | |
| Cerebral Angiogram (DSA) ^ | X# w/3D | X w/3D | | | X w/3D | |
| Adverse Event assessment | | X | X | X | X | X |
| Procedure Information | | X | | | | |
| Aneurysm Occlusion Status – Raymond Roy and general assessment on study form## | | X | | | X | |

^Baseline image aneurysm assessment can be made with either CTA, MRA **OR** DSA, upon MD discretion.

# Baseline image screening can be completed within 3 months prior to enrollment. Imaging will always be performed on the day of the procedure which will be used for core laboratory baseline for comparison at 6 months.

* The NIH Stroke Scale score should be obtained within 24 hours after stroke in the event a subject is diagnosed with a stroke.

** mRS will be obtained at all scheduled visits.

## Aneurysm occlusion status and Raymond Roy completed when cerebral angiograms are performed.

**Background**

The most commonly provided endovascular therapy for intracranial aneuryms (IA) is coil embolization. Endovascular coiling and neurosurgical clipping are therapeutic options, and the outcome in terms of survival free of disability at 1 year is significantly better with endovascular

coiling.[4] Despite the high prevalence of its use, coil embolization success in wide necked bifurcated/side wall aneurysms is limited due to geometric considerations and target intracranial aneurysm access. Coils can become compacted and regress into the dome of the IA due to water hammer effect resulting in further filling at the IA neck.

Two other technologies to support coiling in wide neck aneurysms have emerged; Balloon assisted coiling (BAC) and stent assisted coiling (SAC) which also have their own set of issues.[5]

Balloon assisted coiling is a technique where a balloon is inflated at the neck to create a temporary wall so coils can be deployed to fill the aneurysm without the need for dual antiplatelet. However, this technique has its own challenges as there is a need to completely close the aneurysm but at the same time protect different branches of the bifurcation. Risk factors including procedure-related complications leading to death or dependency were significantly higher in BAC (14.1%) compared with those in conventional coiling (3%).[6]

Stent assisted coiling consists of two techniques; Y stenting and waffle cone, both of which consist of creating a permanent scaffold in the parent vessel to support coils inside the aneurysm sac. Unfortunately, both of these techniques can only be used in unruptured or recanalized aneurysms as dual antiplatelet therapy is required to avoid stent thrombosis. Risk factors were associated with a significant decrease of angiographic recurrences, but they were associated with more lethal complications compared with coiling without stents.[7]

More recently, new devices for IA treatment that retard the flow of blood from the parent artery into the IA, have become available. Flow diverters are high mesh density stents placed in the parent artery across the neck of the IA. Stasis of blood in the IA induces thrombosis which helps achieve the goal of preventing pulsatile flow into the IA. The mesh component of flow diverters has also

[4] Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RS. The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT). The Lancet. 2015 Feb 27;385(9969):691-7.

[5] L Pierot. A Biondi (2006) Endovascular techniques for the management of wide-neck intracranial aneurysms: A critical review of the literature. J Neuroradiology. 2016 Jun;43(3): 167-75. Doi: 10.1016/j.neurad.2016.02.001.Epub 2016 Mar 11.

[6] Sluzewski M, van Rooij WJ, Beute GN, Nukssen PC. Balloon-assisted coil embolization of intracranial aneurysms: incidence, complications, and angiography results. J Neurosurgery. Sep; 105(3):396-9.

[7] Piotin M, Blanc R, Spelle L, Mounayer C, Piantino R, Schmidt PJ, Moret J. (20xx) Stent-Assisted Coiling of Intracranial Aneurysms Clinical and Angiographic Results in 216 Consecutive Aneurysms. Stroke. 2010 Jan;41(1):110-5. Doi:10.1161/STROKEAHA.109.558114.Epub 2009 Dec 3.

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| | 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-endothelialization) distinguish flow diverters from standard coil embolization used with or without adjunctive devices.<br><br>Published data demonstrates high occlusion rates for aneurysms treated with flow diverters, irrespective of aneurysm size, with the complete occlusion rate reaching >50% at 6 months and > 80% at 1 year. Morbidity, thromboembolic complications, and mortality associated with the |

[8] Kallmes, D. F., et al. (2009) A second-generation, endoluminal, flow-disrupting device for treatment of saccular aneurysms. AJNR Am. 30(6):1153-8

treatment of unruptured aneurysms with flow diversion have been comparable with that reported in stent-assisted coiling literature. In addition, recent cost-effectiveness analyses have favored flow diversion over alternative endovascular treatments, particularly for large or giant aneurysms.[9]

An attempt to establish a faster procedure, which would not require anticoagulation and antiaggregation and to improve the stability of aneurysm occlusion prompted the recent development of intrasaccular flow disruptors.[10] The Contour is a flow diverter designed to be placed in the IA sac. Like other flow diverters, the device is designed to disrupt blood flow into the IA and to provide a stablea scaffold for the establishment where endothelial cells can grow. These two mechanisms of action may increase the likelihood of complete IA occlusion compared to embolization coils.

Two intrasaccular flow diverters have received CE-mark, but only one is available for clinical use in Europe. The WEB is a mesh device in a spherical shape. It works by mechanisms similar to Contour in that 1) it is an intrasaccular flow diverter, and 2) its mesh can serve as a scaffold upon which endothelial cells can grow, however, difficulty in accurate sizing and resulting compaction of the device may limit long term success rates.[11] Significant clinical experience is already available for WEB. The device in its first version with two mesh layers ("dual layer") is no longer available. A single layer version with a more spherical shape comes with a lower profile, enhanced visibility, better navigation and is offered in diameters of 4–11 mm. WEB can be used with a high level of procedural safety. Early aneurysm occlusion is achieved in the majority of aneurysms. The

[9] Fargen, K. M. and B. L. Hoh (2015). "Flow Diversion Technologies in Evolution: A Review of the First Two Generations of Flow Diversion Devices." World Neurosurg 84(2): 254-256

[10] Mine, B., et al. (2014). "Intrasaccular flow-diversion for treatment of intracranial aneurysms: the Woven EndoBridge." Expert Rev Med Devices 11(3): 315-325

[11] Cognard, C. & Januel, A. C. (2015). Remnants and Recurrences After the Use of the WEB Intrasaccular Device in Large-Neck Bifurcation Aneurysms. Neurosurgery 76, 522–530

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| | issue of aneurysm recurrence, however, is not solved with this implant as it appears that the device can experience changes in shape and configuration leading to aneurysm recanalization.[12]<br><br>Another intrasaccular flow diverter, Artisse, also consists of a double layer of nitinol wire mesh held together by two radiopaque markers. It was primarily designed to treat small-necked aneurysms, and the only available shape is oval. The device is currently under clinical evaluation and no clinical and anatomical results have been published to date.<br><br>The Contour Neurovascular System™ provides improvements and several advantages in the field of vascular occlusion devices because it provides aneurysm treatment and/or amelioration, particularly for neurovascular aneurysms, via the use of a minimum amount of fully-retrievable deployable material. Its configuration eliminates the need for additional material for pinning the aneurysm neck and/or for an anchoring mechanism in the parent vessel adjacent to the aneurysm and/or for spherical, radial expansion of the body portion of the device into the sac of the aneurysm. |

# 3 Acronyms

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

[12] Williamson, R. W., et al. (2015). "Intrasaccular Flow Diversion for Wide-Neck Bifurcation Aneurysms: Should the Bar Be Set Higher?" World Neurosurg 84(2): 207-208

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| AE | Adverse event |
| ADE | Adverse device effect |
| CA | Competent Authority |
| CIP | Clinical Investigation Plan |
| CRF | Case report form |
| CRO | Contract Research Organization |
| CT | Computed Tomography |
| CTA | Computed Tomography Angiography |
| CTA | Clinical Trial Agreement |
| CVA | Cerebrovascular accident |
| DPW | Detachable Pusher Wire |
| EC DSA | Ethics Committee<br>Digital Subtraction Angiography |
| GCP | Good Clinical Practice |
| IA | Intracranial Aneurysm |
| IC | Informed consent |
| ICF | Informed consent form |
| ID | Identification |
| LTF | Lost to Follow-up |
| MC | Microcatheter |
| MR | Magnetic resonance |
| MRI | Magnetic resonance imaging |
| MRA | Magnetic resonance angiogram |
| mRS | Modified Rankin Scale |
| NIH | National Institutes of Health |
| PI | Principal Investigator |
| SADE | Serious adverse device effect |
| SAE | Serious adverse event |
| SAH | Subarachnoid haemorrhage |
| TOF | Time-of-flight |
| USADE | Unanticipated Serious Adverse Device Effect |

# 4 Introduction

Intracranial aneurysms (IA) 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 widenecked 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 heatset 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 endothelialization can occur. 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. Migration of the device is associated with movement out of the aneurysm sac, whereas movement refers to movement distally into the sac. 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 study was designed in accordance with International Organization for Standardization (ISO) 14155:2011, the World Medical Association (WMA), Declaration of Helsinki in its current version and MEDDEVs from the European Commission.[12-19]

# 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"), 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 2 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 (IFU) for additional information.

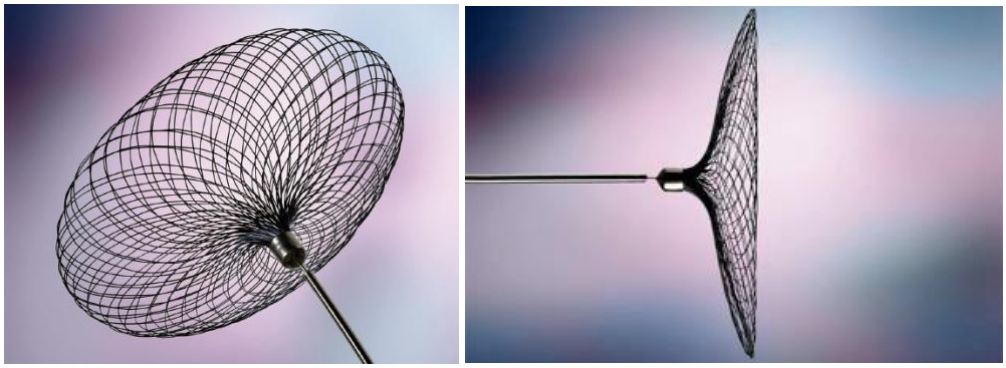

Figure 2. Contour Neurovascular System™ Implant

## 5.2 Indications for Use and Intended Use

The Contour is intended for the endovascular embolization of unruptured intracranial aneurysms. The device should only be used by physicians licensed and credentialed to perform endovascular embolization catheterization procedures. Physicians must be thoroughly familiar and experienced with standard vascular embolization techniques and the Contour Neurovascular System™ before using the device.

The Contour is placed across the neck of the aneurysm and acts as both a flow disrupter and a flow diverter. The device mesh provides a scaffold distributed across the neck of the aneurysm for the establishment of neointimal development resulting in aneurysm occlusion.

## 5.3 Training

Cerus Endovascular will provide training to all participating investigators using a variety of the following:

- flow models
- didactic slide presentation
- implant simulation using a vascular simulation 3-D replicator

A patient selection committee will provide guidance over the identification of all suitable aneurysms in all eligible patients at each site to facilitate successful patient identification and implantation. The patient selection committee consists of 3 or more implanting physicians from around the world who are trained and/or experienced with Contour and have previous experience with embolization devices used in aneurysm treatment. The committee will have access to the patient images submitted by the investigator during the screening process. The selection committee will individually review and cast opinion on whether the proposed anuerym is treatable with a Contour device per product specification guidelines. The web-based image system called CIMAR will be used to view and store images and patient committee member opinions on aneurysm suitability for treatment based on the Contour sizing guidelines.

Physician proctoring by a consulting clinician will occur for the first three implants at a newly implanting center. The proctor will provide feedback and guidance for the implantation of the Contour after the selection committee determines the aneurysm is treatable. A sponsor representative will also be available for at least the initial six implantation procedures.

## 5.4 Device Manufacturing Overview

The Contour Neurovascular System is manufactured by Cerus Endovascular, Ltd., 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.

## 5.5 Device Evaluation and Testing

### 5.5.1 Biocompatibility and Biological Safety

A biological risk assessment of the Contour Neurovascular System has been performed. This assessmentfocused on the requirements of EN ISO 10993-1:2009, EN ISO 14971:2012, and the European Union (EU)Medical Device Directive (MDD) 93/42/EEC. The assessment examined the components used in the device, information on device materials from the literature, results of in vitro biocompatibility testing and in vivo studies on the device, and the history of safe and effective use of the device materials in humans. The assessment concluded that Contour Neurovascular System poses a low to rare risk of discernible toxicity to the patient.

# 6 Risks and Benefits

## 6.1 Potential Risks

The potential risks and complications of the device will be explained to the patients receiving the implanted device. The risks similar to the risks of other devices approved for endovascular aneurysm treatment are well known.

These risks may cause significant neurologic complications such as a cerebrovascular accident (CVA) and possibly death, and include but are not limited to the following: infection, abnormal bleeding or clotting, pain, injury to the groin site, injury to the aneurysm including bleeding and/or rupture, decreased blood flow to the brain or other parts of the body, inability of the device to totally prevent blood from flowing inside it, movement of the device within the aneurysms or to another location in the body.

| **Anticipated Risk by Clinical Category** | **Percent Anticipated Risk Occurence** | **Specific Anticipated Risks** |
|---|---|---|
| Neurovascular Sequelae | Rarely (< 5%) | CVA – ischemic |
| | Rarely (< 5%) | CVA – hemorrhagic |
| | Rarely (< 5%) | Aneurysm rupture |

| **Anticipated Risk by Clinical Category** | **Percent Anticipated Risk Occurence** | **Specific Anticipated Risks** |
|---|---|---|
| | Rarely (< 5%) | Blood vessel dissection |
| | Rarely (< 5%) | Blood vessel perforation/rupture |
| | Rarely (< 5%) | Subarachnoid hemorrhage |
| | Rarely (< 5%) | Parenchymatous hematoma |
| | Rarely (< 5%) | Intraventricular hemorrhage |
| | Rarely (< 5%) | Thrombosis with resultant occlusion of aneurysm parent artery of other blood vessel |
| | Rarely (< 5%) | Embolism with resultant occlusion of blood vessel |

| | | |
|---|---|---|
| | Less Likely (5-15%) | Device migration – from the aneurysm to a distal site |
| | Likely (>15%) | Headache |
| | Rarely (< 5%) | Cranial nerve palsy |
| | Rarely (< 5%) | Intra-cranial hypertension |
| | Less Likely (5-15%) | Recanalization of the aneurysm |
| Vascular Access Site Sequelae | Less Likely (5-15%) | Bleeding/Hematoma |
| | Very Rarely (< 3%) | Local infection |
| | Less Likely (5-15%) | Pseudoaneurysm |
| | Rarely (< 5%) | Thrombosis with resultant occlusion of access artery |
| | Rarely (< 5%) | Embolism with resultant occlusion of blood vessel |
| | Rarely (< 5%) | Arterio-venous fistula |
| **Anticipated Risk by Clinical Category** | **Percent Anticipated Risk Occurence** | **Specific Anticipated Risks** |
| Angiogram-related Sequelae | Less Likely (5-15%) | Allergic reaction to contrast media |

| | | |
|---|---|---|
| | Less Likely (5-15%) | Radiation exposure – the radiation dose of 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). Exposure of the fetus to radiation can harm the fetus and shall be avoided. In addition, if the subject is of childbearing age, the doctor will ask the subject to undergo urine or blood pregnancy tests at the time of the procedure or angiograms to ensure that the subject is not pregnant. |
| | Less Likely (5-15%) | Renal dysfunction secondary to contrast media |
| Other Risks | Less Likely (5-15%) | Non-allergic drug reaction (local or systemic) |
| | Less Likely (5-15%) | Allergic drug reaction |
| | Rarely (< 5%) | Bleeding event – non-intracranial, non-access |
| | Rarely (< 5%) | Cardiovascular events |
| | Rarely (< 5%) | Peripheral vascular events |
| | Rarely (< 5%) | Gastrointestinal events |

### 6.1.1 Risk Mitigation

The manners in which risks shall be minimized for the device procedure include the following:

1. The PI and clinical site staff were chosen because of their expertise in the field of neurovascular procedures.
2. The physician(s) performing device-related procedures have received the appropriate training in the use of the device.
3. Subjects are being monitored/observed throughout the study by multiple-disciplinary site staff, trained in the management of patients with IAs.
4. Extensive pre-clinical, bench and *in vivo* testing was performed in order to optimize the device safety and function.
5. Sponsor Clinical Personnel shall provide oversight throughout the Study.

There may be unknown risks.Experienced Clinical Monitors will perform on-site and remote Monitoring throughout the trial to ensure protocol compliance and compliance with ISO 14155:2011 and all applicable EC and competent authority (CA) regulations.

## 6.2 Potential Benefits

There may be no direct benefit for subjects participating in this study. Subjects may indirectly benefit from their participation in this study by helping researchers improve their understanding of the Contour Neurovascular System. This study allows the Sponsor and Investigators to help other patients indicated for similar procedures.

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. Therefore, subjects may potential show a benefit if they have complete IA occlusion from the Contour Neurovascular System. This may reduce the risk of subsequent IA rupture.

In addition, potential benefits that may be associated with endovascular treatment of IAs include:

- Less invasive approach to treatment compared to surgery
- No surgical incisions required, avoiding complications associated with surgical clipping
- Decrease in post-operative morbidity caused by surgical procedures performed under general anesthesia
- Less operative discomfort
- Reduced total procedure time compared to surgical clipping
- Shorter hospital stay

Possible benefits of the Contour Neurovascular System vs. standard endovascular aneurysm coiling:

- Simplified sizing approach
- Reduced operative time
- Reduced risk of rupture since the device does not engagre with the vulnerable aneurysm dome during the procedure
- Ability to stabilize device in optimal placement with the visualization feature on the DPW which can visually confirm separation of implant from device after detachment
- Controlled deployment and placement with the ability to be deployed and re-sheathed multiple times in a safe and controlled manner until optimal placement is achieved • Reduced exposure to radiation
- Improved durability of embolization by creating a stable scaffold across the aneurysm neck to permit establishment of stable endothelium.
- Ability to confirm device stability upon implant by device oversizing to the aneurysm and employing a ‘push’ technique with the DPW prior to final detachment
- Lower total mass of implanted material thus reducing the “mass effect” on adjacent structures in the brain.

## 6.3 Risk-to-Benefit Rationale

The Contour Neurovascular System has been implanted in first-in-human, pilot studies and compassionate use patients. The device has been proven to be suitable for its intended purpose. There are no unacceptable residual risks/intolerable risks beyond the need to evaluate the safety and performance within this protocol. All applicable anticipated risks have been addressed through the provision of the appropriate IFU. Evaluation of the risks and benefits that are expected to be associated with the use of the Contour Neurovascular System demonstrate that when used under the conditions intended, the benefits associated with the use of the Contour Neurovascular System should outweigh the risks.

# 7 Investigational Protocol

## 7.1 Design

Prospective, single arm, multi-center study. Details are provided in Section 10 – Statistical Analysis.

## 7.2 Objective

The primary objective of this study is to document the safety and performance of the Contour Neurovascular System™. The data from the study will be reported as a Pre-Market study to the Notified Body to support CE Mark approval. In addition, the data may be used to support US approval by the Food and Drug Administration (FDA) to market the Contour device in the United States.

## 7.3 Target Patient Population

The target patient population is patients with unruptured intracranial aneuryms requiring endovascular treatment.

## 7.4 Screening

Patients shall 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. Only unruptured IAs will be included in the study. A detailed list of the eligibility criteria is included in the Eligibility Section.

Screening includes a clinical evaluation and a review of appropriate imaging which typically includes a computed tomography angiography (CTA), magnetic resonance angiogram (MRA) and/or a cerebral angiogram (DSA), which are all standard of care for patients who have been diagnosed with or are suspected to have an IA. It is recommended that the baseline screening angiogram include the acquisition of a 3D rotational angiogram of the aneurysm and parent vessel for proper evaluation of the anatomy. The angiogram completed at the time of procedure can be used for the Baseline Angiogram.

## 7.5 Eligibility

To participate, patients must meet all inclusion criteria and no exclusion criteria listed in Table ***3***.

**Table 3. Study Eligibility Criteria**

Inclusion Criteria

Patients of all genders who meet all indications and contraindications will proceed to implantation.

1. Patient's indication for treatment of unruptured aneurysm is according to the national/international guidelines.
2. Age 18-80 years at screening
3. Patients who are suitable for nonemergency endovascular embolization of saccular IAs
4. IA located at a bifurcaton in the anterior or posterior circulation with dimensions consistent with implant size selection guidelines included in the IFU
5. 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
6. Patient able to able to give their informed consent can be included in this study. This must be demonstrated by means of a personally signed and dated informed consent document indicating that the subject has been informed of and understood all pertinent aspects of the study.

Exclusion Criteria

The presence of condition that may create unacceptable risk during the aneurysm embolization procedure, such as patients with:

1. Ruptured aneurysm
2. Patient anatomy or physiology considered unsuitable for endovascular treatment
3. Contraindication for arterial access
4. Largest measured IA equatorial diameter >8.5 mm or <2 mm
5. Largest measured IA neck diameter >8 mm or <2 mm
6. Target IA contains other devices/implants (e.g., coils)
7. Known allergy to platinum, nickel or titanium
8. Known allergy to contrast agents
9. Contraindication to anticoagulants or platelet inhibitor medication
10. Stenosis of the target IA's parent vessel >50%
11. Anticoagulation medications such as warfarin that cannot be discontinued.
12. Pregnant, breastfeeding or planning pregnancy in the next 2 years
13. Acute / chronic renal failure (including dialysis); Creatinine > 2.00 mg/dl or > 182 µmol/L
14. Myocardial Infarction, Stroke or TIA within the last 6 months
15. Any other medical issue within the brain that precludes the device implantation such as brain surgery, radiation in the target area of intervention, acute traumatic craniocerebral injury, etc.
16. Other medical conditions that cause an inability to comply with study requirements and/or that could increase the risk of neurovascular procedures or death within 2 years (e.g., liver failure, cancer, heart failure, chronic obstructive pulmonary disease, immunosuppression, neural disease, and hematologic disorders etc.)
17. Participating in another study with investigational devices or drugs that would confound the effects of the study outcomes

All patients must sign a study-specific consent form prior to the commencement of any protocol-specific assessments and/or procedures. Final qualification will occur during the implant procedure due to the need for confirmation of IA appropriateness with cerebral angiography.

The patient is enrolled at the time of consent and is considered a study subject in the reporting analysis group only when the patient is fully qualified and at least one Contour device has been placed into the patient's body. The following listing provides examples of patient enrollment scenarios for the study:

- The patient is not considered enrolled but not included in the primary analysis group in the study: if at the onset of the procedure in the initial DSA, the investigator determined the patient's IA was not suitable for treatment with the device, thus, no attempt was made by the investigator to place the device. The patient will be treated outside of the study per the investigator's usual practices. The reason for not treating the patient must be documented on a study exit form. The patient is not included in the primary analysis group because the Contour was never opened or deployed inside the patient. All patients will be listed in the final report. ○ The patient is considered enrolled but not included in the primary analysis group in the study: at the onset of the procedure, the investigator determined the subject's IA was suitable for treatment with the device. The investigator attempted but was unable to place the 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 1-month visit. All failed implant attempts will be reported in the final report.
- The patient is considered enrolled and included in the primary analysis group in the study: if at the onset of the procedure, the investigator determined the subject's IA was suitable for treatment with the device. The investigator successfully placed the 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.
- The patient is considered enrolled and included in the primary analysis group in the study: if at the onset of the procedure, the investigator determined the subject's IA was suitable for treatment with the device. The investigator successfully placed the 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.

The available sizes of the Contour implant along with coordinating aneurysm dimensions and definitions are provided in Figure 3.

| REF (Catalog 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 |

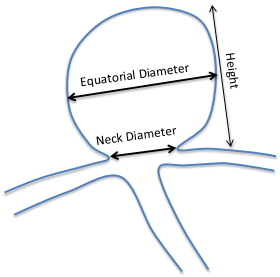


Figure 3 – Contour Sizing and Aneurysm Dimension Definitions

## 7.6 Baseline Evaluation

The baseline evaluation is performed after signing the consent form and prior to the implant 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. A modified Rankin Scale (mRS) will be performed 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.

All images obtained at screening or from images obtained prior to screening as standard, including the 3D angiogram, MRA and/or CTA are to be submitted for review to the patient selection committee 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 committee. Additionally, the images obtained at baseline shall be submitted to the independent core laboratory.

### 7.6.1 Angiogram

A cerebral angiogram that includes a 3D rotational angiogram shall be performed prior to 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. Imaging will always be performed on the day of the procedure which will be used for core laboratory baseline for comparison at 6 months. All imaging must be submitted to the independent core lab for analysis.

## 7.7 Implant Procedure

### 7.7.1 Preoperative Preparation

The subject undergoes standard preoperative preparation. The device implant 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, distal support guides) 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.

### 7.7.4 Contour Neurovascular System™ Procedure

Contour Neurovascular System placement is described in detail in the Instructions for Use (IFU). Briefly, the target IA is accessed via standard methods. A 0.027" microcatheter is placed into the target IA. The Contour Neurovascular SystemTM device is introduced into the microcatheter and slowly delivered into the target IA. Once the Contour implant is in the appropriate location, the device positioning and stability is confirmed via a gentle push forward on the DPW, then 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, shall be submitted to the independent core laboratory.

Pre and 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

Following discharge, the subject will have a follow-up visit at 1 month, 6 months and 12 months after the implant procedure. At each study visit, the subject shall be assessed for any new adverse events (AEs). 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

assessment should be obtained within 24 hour after a stroke in the event a subject is diagnosed with a stroke. Cerebral angiography will be repeated at 6 months. The cerebral angiography will include a 3D angiogram. 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 shall be evaluated by an independent core laboratory.

The study's schedule of assessments and post-treatment visit windows are shown in Table 4.

Table 4. Schedule of Assessments

| | Baseline[#] | Procedure | Discharge | 1-month ) 1 weeks | months ) 1 month | 12 months ) 1 month |
|---|---|---|---|---|---|---|
| Medical history and medications | X | | | | | X |
| Neurologic Exam | X | | X | X | X | X |
| NIH Stroke Scale | X | X[*] | X[*] | X[*] | X[*] | X |
| Modified Rankin Scale (mRS) | X | | X[**] | X[**] | X[**] | X |
| Pregnancy test (pre-menopausal female) | X | | | | | |
| CT angiography (CTA) ^ | X[#] | | | | | |
| Magnetic Resonance Angiogram (MRA) ^ | X[#] | | | | | |
| Cerebral Angiogram (DSA) ^ | X[#] w/3D | X w/3D | | | X w/3D | |
| Adverse Event assessment | | X | X | X | X | X |
| Procedure Information | | X | | | | |
| Aneurysm Occlusion Status – Raymond Roy and general assessment on study form[##] | | X | | | X | |

^Baseline image aneurysm assessment can be made with either CTA, MRA **OR** DSA, upon MD discretion.

# Baseline image screening can be completed within 3 months prior to enrollment. Imaging will always be performed on the day of the procedure which will be used for core laboratory baseline for comparison at 6 months. * The NIH Stroke Scale score should be obtained within 24 hours after stroke in the event a subject is diagnosed with a stroke.

** mRS will be obtained at all scheduled visits.

## Aneurysm occlusion status and Raymond Roy completed when cerebral angiograms are performed.

## 7.10 Early Withdrawal

Reasons for subject withdrawal prior to study completion shall be documented. Valid reasons for early study withdrawal include:

- Death
- AE or other medical condition that prevents study participation
- Withdrawal of voluntary consent
- Lost to follow-up (LTF)
- Termination of Study

At least three documented attempts shall be made to contact any subject who is LTF.

## 7.11 Study Termination

The Sponsor has the right to terminate the Study. Reasons for Study termination shall be documented in the Clinical Investigation Report and Close-Out Monitoring Report. Valid reasons for study termination include:

- Administrative issues mandate termination
- Interim data analyses warrant study termination
- Regulatory action mandates termination

If the study is terminated for any reason, the governing Competent Authority and Ethics Committee shall be notified as applicable. If the study is terminated, all patients will remain in follow-up per the standard of care.

## 7.12 Premature termination

The Sponsor reserves the right to discontinue the clinical trial/investigation at any stage (e.g. for safety reasons) or reduce the follow-up period with suitable written notice to the Investigator.

Possible reason(s) include:

Sponsor makes a final decision for the early termination of the clinical trial, or per DSMB recommendation

Further product development is cancelled.

Should the clinical trial be discontinued by the Sponsor, subjects will be followed up as per routine hospital practice.

In this case, the Investigator shall return all clinical trial/investigation materials (including devices) to the Sponsor and provide a written statement as to why the premature termination has taken place to the EC (if applicable) and inform subjects still participating to the trial. All applicable Clinical Investigation documents shall be subject to the same retention policy (the Investigators and/or designee(s) will be instructed to retain all study records required by the Sponsor and regulatory authorities in a secure and safe facility, with limited access. All study material shall be stored for at least 10 years or as based on national

regulations. The Investigator must request authorization from the Sponsor prior to destroying study records). Sponsor or designee will inform the CA about premature termination of Clinical Trial as per regulatory requirements Study discontinuation:

The Study Completion/Discontinuation Form must be completed when:

- the subject is considered lost to follow-up (per the above definition) before the 12 months follow-up time point has been reached or
- the subject withdraws from the study or
- the Investigator withdraws the subject from the study or
- the subject has completed the study (at last Follow up visit per protocol, the 12 months follow up visit).

*The Sponsor shall be notified of the reason for subject discontinuation. The site will provide this information on the Study Completion/Discontinuation Form (e-CRF) and on source documents. Investigators must also report this to their EC if defined by their institution's procedure.*

# 8 Adverse Events

## 8.1 Adverse Event Definitions

Definitions of Adverse Event subtypes are provided in Table 5. All AEs and device deficiencies shall be reported by the clinical site investigator on a specific case report form (CRF).

Table 5. AE Definitions per ISO 14155:2011

| | |
|---|---|
| Adverse Event (AE) | An AE is:<br>Any untoward medical occurrence in a subject, 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.<br>Note 1: This definition includes events related to the investigational medical device or the comparator.<br>Note 2: This definition includes events ralted to the procedures involved.<br>Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices. |
| Adverse device effect (ADE) | An ADE is:<br>AE related to the use of a 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 medical device.

Serious adverse event (SAE)

An SAE is: an

AE 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 fetal distress, fetal death, or a congenital abnormality, or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered to be an SAE.

Serious adverse device effect (SADE)

An SADE is:

ADE that has resulted in any of the consequences characteristic of an SAE.

Unanticipated serious adverse device effect (USADE)

A USADE is:

a SADE 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.

## 8.2 Adverse Event Classification

### 8.2.1 **AE Severity:**

The severity of an AE is a qualitative judgment of the degree of intensity, as determined by the Investigator or as reported by the subject. The severity of the AE shall be evaluated according to the following scale:

- Mild - no limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
- Moderate - some limitation of usual activities or specific therapy is required.
- Severe - inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.

The assessment of severity shall be made independent of the relationship to the device and therapy or the seriousness of the event.

### 8.2.2 AE causality:

Each AE shall be assessed by the Investigator for its relationship to the use of the study device or study procedure as outlined below.

**Device Related:** Restricted to the study device.

**Procedure Related:** Restricted to the implant procedure and any procedure associated directly with placement of the device.

**Definitely related:** An AE is definitely related to a specific category if it is obvious, certain or there is little doubt regarding the relationship.

**Possible related:** An AE is possibly related to a specific category if it is capable of being related but relatively unlikely.

**Not related:** An AE is not related to a specific category if it is determined that there is no plausible association.

Subjects experiencing AEs shall be offered comprehensive medical care for conditions associated with the implant procedures and followed until their medical outcomes are resolved.

Table ***6***. AE Categorization

| **AEs** | **Non-DeviceRelated** | **Device-Related** | | **Device Deficiencies*** |
|---|---|---|---|---|
| Non-Serious | AE | ADE | | Without SADE potential |
| Serious | SAE | SADE | | With SADE potential |
| | | Anticipated | Unanticipated | |

| | | | | |
|---|---|---|---|---|
| | | ASADE | USADE | |

* Device deficiency is the inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, misuse, errors, inadequate labeling

## 8.3 Adverse Event Reporting/Analysis

The timely and complete reporting of AEs is essential for the risk management process. Monitoring and documentation of all AEs will allow the Sponsor to identify potential ADEs and to adhere to regulatory requirements.

The Investigative Site shall report all SAEs including USADEs and device deficiencies to the study sponsor or the sponsor's designee within 48 hours of occurrence.

All AEs shall be documented in the patient's medical record by the PI and reported by the PI using the AE CRFs. AE definitions and categories are described in Section (8), the Monitors shall confirm that the AEs

are correctly categorized and entered onto the AE CRFs. The Monitor shall confirm that the AEs are consistent with the source documents.

The sponsor is responsible for submitting reports to the Competent Authority as required by the applicable regulations and guidelines. The investigator is responsible for reporting safety information to the ECs according to the ECs requirements.

# 9 Study Oversight

## 9.1 Clinical Events Committee (CEC)

A CEC will be established by Cerus Endovascular or designee to assess, review and classify all neurologic, device-related and procedure-related SAEs to ensure they are reported accurately. The CEC member(s) appointed for the study will be qualified by background, training and expertise in neurovascular treatment of IAs. The member(s) will not be an investigator on the study. The CEC will regularly review and adjudicate the adverse events and any deaths. Classification of the events will include device and procedure relatedness and seriousness. Member(s) will be provided data summaries and source documentation for review.

## 9.2 Data Safety and Monitoring Board (DSMB)

A DSMB will convene of member(s) experienced in an associated disclipline. The DSMB will review the study data after enrollment of the first five patients. Enrollment of further patients will occur as the DSMB reviews the data. The DSMB will provide a report following the review and advise Cerus Endovascular for any modifications or concerns that may be necessary. The DSMB will provide further evaluation at least twice per year and after the first 5 patients are enrolled. If slow enrollment occurs, the DSMB may meet less frequently. The CEC and DSMB will meet as a combined committee.

## 9.3 Patient Selection Committee

A patient selection committee will provide guidance over the identification of all aneurysms in all eligible patients at each site to facilitate successful patient identification and implantation. The patient selection committee consists of 3 or more implanting physicians from around the world who are trained and/or experienced with Contour and have previous experience with embolization devices used in aneurysm treatment. The committee will have access to the patient images submitted by the investigator during the screening process. The selection committee will individually review and cast opinion on whether the proposed anuerym is treatable with a Contour device per product specification guidelines. The web-based image system called CIMAR will be used to view and store images and patient committee member opinions on aneurysm suitability for treatment based on the Contour sizing guidelines.

# 10 Statistical Analysis

This study intends to examine the safety and performance of the Contour Neurovascular System TM used for the treatment for embolization of intracranial anueryms. The data from the study will be reported as a Pre-CE Mark study to the Notified Body to support CE Mark approval. In addition, the data may be used to support US approval by the Food and Drug Administration (FDA) to market the Contour device in the United States. The study is not powered to detect statistical significance. As such, clinical judgement is required to assess device safety and performance from the data collected during this study. Clinical judgement will be provided throughout the study by the DSMB. In addition, under future review of the Clinical Section of the regulatory submission for CE Mark, clinical review will be included from the Notified Body to ensure adequate documentation of safety and performance required for the CE Mark.

## 10.1 Justification of Methodology

This study is designed as a single arm study to develop further understanding of the Contour Neurovascular System. It will provide safety and performance information for subjects from the Contour implantation to six month follow-up.

At one month post procedure, the subjects will provide an adverse event profile related to the placement of the device. At six months of the study there will be additional information related to the adverse event profile including any device related instability or deficiency.

Similarly, the subjects will provide a performance profile. At six months post procedure, the information will provide how well the aneurysm has healed or embolized through the analysis of imaging performed by the independent core lab for accuracy and removal of bias.

The totality of the data will represent the data necessary for submission to the Notified Body for the assessment of CE Mark application.

## 10.2 Patient Population

Two patient populations will be considered in the analyses, an Intent-to-Treat (ITT) population and a Per Protocol population (PP). The ITT population includes all patients. The PP population will include subjects who complete 6 months of follow-up, die prior to their 6-month clinic visit, or are study failure (withdrawal from study to obtain alternate treatment). The PP will exclude patients with any major protocol violation that affects proper study inclusion or significant outcomes. Endpoints will be evaluated in the PP and ITT populations.

## 10.3 General Principles

The analysis for all primary and secondary study endpoints and baseline, procedural and follow-up characteristics will be performed on an intent-to-treat analysis population which will include all available data for all enrolled subjects. Standard summary statistics will be calculated for all study variables.

The primary safety endpoint will be calculated as the proportion of subjects with death of any nonaccidental cause or any major stroke within the first 30 days after treatment or major stroke or death due to neurological case from day 31 to 6 months after treatment.

The primary performance endpoint will be calculated as the proportion of subjects with complete occlusion demonstrated with a Grade 1 on the Raymond Roy Scale at 6 months.

For AE reporting, both subject counts and event counts will be presented in tabular summaries of results.

A summary of subjects with protocol deviations will be reported but those subjects will be included in all analyses although endpoints may be summarized without the subjects (per-protocol analysis group) to provide additional information but not for the primary analysis.

For continuous variables, statistics will include means, standard deviations, medians and ranges. Categorical variables will be summarized in frequency distributions. Missing data will not be imputed. The number of data values available for each analysis will be reported so that the impact of missing data can be seen.

Statistical analyses will be conducted in SAS version 9.4 or above (SAS Institute, Cary, N.C.).

## 10.4 Multi-center Trial Considerations

Up to 10 clinical sites will participate in the study. The maximum enrollment at any one site will be 20 subjects.

This is a multi-center clinical study with standardization of subject enrollment, data entry and AE reporting.

## 10.5 Endpoints

### 10.5.1 Primary Endpoints

**Primary Safety Endpoint:**

The proportion of subjects with death of any non-accidental cause or any major disabling stroke within the first 30 days after treatment or major disabling stroke or death due to neurological cause from day 31 to 6 months after treatment.

Note: Major Disabling Stroke is defined as an episode of neurological signs or symptoms that persist beyond 24 hours accompanied with evidence of ischemia/infarction on imaging that results in an increase of NIHSS from baseline by $^{3}$ 4 points and/or an increase from mRS baseline by >2.

**Primary Performance Endpoint:**

To demonstrate the occlusion rate on the 6 month angiogram as adjudicated by a core laboratory. Success will be defined as complete occlusion demonstrated by a Grade 1 using the Raymond Roy Scale.

### 10.5.2 Secondary Endpoints

Additional measures will be summarized:

**Secondary Safety Endpoint:**

- Serious Adverse Events (SAE) associated with the procedure or device
- All serious neurological adverse events **Secondary Performance Endpoint:**
- Detailed assessment of aneurysm occlusion from Post Procedure to 6-months provided by the core lab review of the angiogram (DSA) including the following:
  - Raymond Roy scale
  - Modified Web Occlusion Scale
  - Percent Occlusion
  - Device Stability
- Rate of retreatment
- Summary of device performance including the following:
  - Time required for implantation of the Contour
  - Device sizes used
  - Number of attempts to deploy the device
  - Number of failed implant attempts
  - Any reports of device deficiencies

### 10.5.3 Independent Analysis of Imaging

Follow-up imaging (i.e., cerebral angiograms) angiographic assessments of the aneurysm shall 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 shall not be affiliated with a clinical study site.

## 10.6 Interim Analysis

No interim data analysis will be performed.

## 10.7 Sample Size Rationale

This is a single arm study designed to provide adequate data for the purpose of CE Mark. It is expected the 30 patients with evaluable data at 6 month follow-up will show adequate evidence of safety and performance for the application for CE Mark of the device. No formal hypothesis testing of the study endpoints will be performed, therefore no formal sample size was calculated.

# 11 Additional Trial Characteristics

## 11.1 Measures Taken to Avoid Bias

The study has been designed to ensure treatment and follow-up of subjects are consistent with current medical practice.

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.

All investigators must disclose potential conflicts of interest, including financial interests, to the study sponsor prior to participation in the study.

Data from all investigative sites will be monitored throughout the study.

A CEC/DSMB will adjudicate all neurological, device related and procedure related serious adverse events.

A CEC/DSMB will regulatory review the study data to provide oversight and necessary input for any trial modifications.

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.

## 11.2 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.

## 11.3 Procedure for Replacing Withdrawn Subjects

Subjects who withdraw from the study shall not be replaced.

## 11.4 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.

## 11.5 Total Expected Trial Duration

The enrollment period is expected to take 9 months and the follow-up duration is expected to be 6 months to obtain data for the primary analysis. The study population will include 30 subjects enrolled and implanted at up to 10 centers in Europe with evaluable data at 6 months for the analysis for CE Mark. It is expected that the study will take 9 months to enroll the first 30 patients and continue up to 9 months for the initial report for CE Mark.

All patients must be consented prior to performing study related procedures. All patients that provide consent and are implanted will be followed according to the follow-up schedule. Any patient for whom a failed implant attempt is performed will be followed for 1-month or until resolution of any potential device or implanted related adverse events, whichever occurs last.

# 12 Study Management

This study will be managed according to ISO 14155:2011, the Declaration of Helsinki in its current revision, 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.

## 12.1 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-to-day 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.

### 12.1.1 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.

### 12.1.2 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 12.1.1.

### 12.1.3 Communications with EC

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

### 12.1.4 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 14155:2011, 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
- either he/she or an authorized designee conducts the consent process consistent with ISO 14155

### 12.1.5 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 on site.

### 12.1.6 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 14155:2011, 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 if required
- not deviate from the CIP, except to maintain the subject's rights, protect the life and physical well-being of a subject in an emergency, or the scientific integrity of the investigation
- document all deviations from the CIP[13]
- ensure that the site has adequate staff and capabilities
- ensure that site equipment used in the study is maintained and calibrated
- 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

### 12.1.7 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

[13] The sponsor may also document deviations from the CIP

- 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, angiograms) must be filed with the patient's records

### 12.1.8 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.

### 12.1.9 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.

### 12.1.10 Medical Care

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

- Informing the subject of a plan for further treatment including the treatment if the device is not implanted
- 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

### 12.1.11 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
- submit a summary of the progress of the study to the involved ethics committee once a year or according to the national/local requirements

### 12.1.12 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.

### 12.1.13 Recording Data on Electronic CRFs

The data will be entered via electronic interface through an Electronic Data Capture system (database), validated and secured with compliant requirements such as audit trail, secure log-in with the PI responsible for reviewing the electronic data and signing using the database system signature method.

The study will use electronic case report forms that have been standardized for the study to collect data. Site personnel will be trained in use of the eCRFs before study initiation. The PI will ensure that data recorded in the eCRFs in a timely manner and are accurate, consistent with source documents, reliable and logically correct.

Electronic CRF Form samples are in Appendix D20.

### 12.1.14 Deviations

The investigator is not allowed to deviate from the Clinical Investigational Plan, except to maintain the subject's rights, protect the life and physical well-being of a subject in an emergency, or the scientific integrity of the investigation. All protocol deviations shall be documented on the Protocol Deviation Case Report Form.

The sponsor (or delegate) is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the Clinical Investigational Plan, conduct additional training, or terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in

some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

#### 12.1.15 Final Report

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

#### 12.1.16 Document Retention

The PI will maintain documents related to this investigation until 2 years after the study is complete or in accordance to EU or individual site requirements. 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).

#### 12.1.17 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.

## 12.2 Sponsor Responsibilities

#### 12.2.1 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

- providing insurance, in accordance with national regulations, covering the costs of treatment of subjects in the event of the study related injuries.

### 12.2.2 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.

### 12.2.3 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

### 12.2.4 Study Documentation Amendment

The IB, CIP, CRFs, informed consent form and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the CIP shall be agreed upon between the sponsor and principal investigator, or the coordinating investigator. The amendments to the CIP and the subject's informed consent form shall be notified to, or approved by, the EC and regulatory authorities. The version number and date of amendments shall be documented. For non-substantial changes [e.g. minor logistical or administrative changes, telephone numbers, renewal of insurance] not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a simple notification to the EC and, where appropriate, regulatory authorities can be sufficient.

### 12.2.5 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
- has access to an adequate number of subjects on a timely basis Site qualification will be documented.

### 12.2.6 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, if required
- list of EC members or EC assurance number, if required
- 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

### 12.2.7 Monitoring

Monitoring will be performed during the study according to the study Monitoring Plan.

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.

### 12.2.8 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.

### 12.2.9 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.

### 12.2.10 On-Site Monitoring

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

- 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.

### 12.2.11 Study 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
- 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)

### 12.2.12 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.

### 12.2.13 Safety Reporting

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

- ensuring the CEC reviews all serious neurologic, device and procedure related adverse events to ensure they are reported accurately and in sufficient detail
- review and classification 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 and 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.

### 12.2.14 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.

### 12.2.15 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. 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.

### 12.2.16 Resuming a Temporarily Suspended Study

If the sponsor temporarily suspends the study and wishes to resume it, the sponsor will inform the 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.

### 12.2.17 Suspension of Study Center

The Sponsor may discontinue a study center if the center 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.

### 12.2.18 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.

### 12.2.19 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

- 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

### 12.2.20 Document Retention

The sponsor will maintain documents related to this pre-market study as required by applicable regulatory standards and according to the applicable national or local law. Required documents to retain are extensive and are listed in Annex E of ISO 14155:2011.

# 13 Publications

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov.

In accordance with the sponsor's Corporate Policy on the Conduct of Human Subject Research, the sponsor requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a sponsor's study or its results. In accordance with the sponsor's Corporate Policy for the Conduct of Human Subject Research, the sponsor will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. The sponsor adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, sponsor personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

All authorship and contributorship requirements as described above must be followed.

Sponsor involvement in the publication preparation and the sponsor Publication Policy should be discussed with the Principal Investigator(s) and/or Executive Committee at the onset of the project.

The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

Publication status will be posted to the pertinent study listing on clinicaltrials.gov.

# 14 References

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16. MEDDEV 2.12-1 rev7 (2012): Guidelines on a Medical Devices Vigilance System.
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18. WMA Declaration of Helsinki. Ethical Principles of Medical Research Involving Human Subjects. JAMA. 2013 Vol. 310 (20): 2191-2194.
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# 15 Revision History

This section maintains the revision history for the document, including submission history.

Revision A of the document was prepared for initial review for NCA and EC submission.

| Rev | DCO | Change Description | Release Date | Submitted to Ethic Committees |
|---|---|---|---|---|
| A | 0344 | Initial Release | 25 Jan 2018 | Feb 2018 |
| B | 0400 | Revisions based on BfArM and Kiel Ethics Committee responses | 03 Jul 2018 | 4 July 2018 |
| C | 0412 | Revisions based on BfArM response | 15 Aug 2018 | NA |
| C | 0415 | Correction Only: correct header to be same for all pages. Correct Sponsor signature page, #56 | 16 Aug 2018 | 17 Aug 2018 |
| D | 0422 | Added Core lab contact<br>Revisions based on BfArM response | 10 Sep 2018 | Sept 2018 |
| E | 0560 | • Correct Sponsor and manufaturer from Cerus Endovascular, Inc., to Cerus Endovascular, Ltd<br>• Remove Pr Laurent Spelle as PI<br>• Change enrollment period from 6 months to 9 months | 06 Dec 2019 | Dec 2019 |
| F | 0560 | • Update to new core lab contact | 06 Dec 2019 | Dec 2019 |

# 16 APPENDIX A - Statement of Compliance and Signature Page

Clinical Investigation Number: DNX099-01

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

Site Name:

Site Principal Investigator:

(Print Name)

Signed:

Date:

# 17 APPENDIX B - Sponsor Approval Page

Contour Neurovascular System™ European Pre-Market Unruptured Aneurysm Study (CERUS)

**Study Title:** DNX099-01

**CIP Document Number:** F

**CIP Revision:**

**CIP Date:** **06 Dec 2019**

**Signature:** _____

**L. Carol Holt, MS, RN**
**Vice President, Clinical Affairs**
**Cerus Endovascular Inc**
**47757 Fremont Blvd**
**Fremont, CA 94538**
**United States**

# 18 APPENDIX C - German Medical Devices (MPG)

Master document is controlled electronically. Copies are not controlled. Ensure revision is valid before use.

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# *Clinical Investigation Plan*

## *Addendum Germany*

*European Pre-Market Study of the Contour Neurovascular System™*

***Protocol No. DNX099-01***

***Addendum 1 to Protocol No. DNX099-01***
***Date: 25-Jan-2018***

***Cerus Endovascular, Inc.***
***47757 Fremont Blvd***
***Fremont, CA 94538, USA***

***- NOTICE-***

*The information contained in this Clinical Investigational Plan (CIP) is CONFIDENTIAL and PROPRIETARY to Cerus Endovascular Inc. and should not be disclosed to anyone not a recipient or reviewer of this CIP. This study will be conducted in compliance with the Declaration of Helsinki, EN ISO 14155:2011 standard, and MEDDEV 2.7/3 guidance.*



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**PROTOCOL ADDENDUM APPROVAL PAGE**

Carol Holt
Vice President, Clinical Affairs
Cerus Endovascular, Inc .
47757 Fremont Blvd
Fremont, CA 94538
United States

Date

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*European Pre-Market Study of the Contour Neurovascular System™*

***Protocol No. DNX099-01***

**CIP Addendum SIGNATURE PAGE**

I have read this CIP Addendum and agree to adhere to the requirements. I will provide copies of this CIP Addendum and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the device and the conduct of the study.

I will conduct the study in accordance with the CIP, the CIP Addendum, Declaration of Helsinki, EN ISO 14155:2011 standard, and MEDDEV 2.7/3 guidance as well as local regulations, and I accept respective revisions to the CIP approved by authorized personnel of the Sponsor and by regulatory authorities.

_____

Site Principal Investigator (print)

_____ _____

Site Principal Investigator (signature) Date

_____

Institution Name/Location

**ADDENDUM 1.0**

An addendum to the above-named Protocol is being added to be in line with the German Medical Devices Act (MPG).



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## 1. Treatment of subjects

### 1.1 PLAN FOR FURTHER TREATMENT AND CARE OF THE PATIENTS AFTER ENDING THE STUDY

Following completion or premature termination of the clinical study, patients will continue to receive treatment by the physician of their choice according to the routine care of patients with unruptured intracranial aneurysms.

Should the study be prematurely terminated, the ongoing care of patients will be discussed with the Principal Investigators at study centers. A plan for continued care according to patient needs will be considered. EC's and regulatory authorities will be notified in writing in the event of study termination/suspension. Patients participating in the study will be contacted by the research team. Detailed information on how enrolled subjects will be managed thereafter will be provided.

### 1.2 The description of the intended medical procedure and examination methods as well as possible deviations from medical standards

Patients enrolled in this study will be treated in line with the routine care for unruptured intracranial aneurysms. All assessments are considered routine and standard of care for Intracranial aneurysms (IA) patients.

During the screening assessments, the deviations from medical standard are limited to the Informed Consent Process and the eligibility assessment.

The use of the Contour Neurovascular System™ during the endovascular embolization catheterization procedure is specific for study patients. As specified in the protocol, the procedure for preparation, delivery, positioning and retrieval of the Contour Neurovascular System™ shall be conducted in accordance with the Contour Neurovascular System™ IFU, CC005-02.C.

Any study follow-up planned after the use of the Contour Neurovascular System™ is considered routine treatment for unruptured intracranial aneurysms patients, including visit 30 days, 6 months and 1 year after the procedure, which does not cause any additional burden or risk for the patient.

## 2. Safety

### 2.1 SAFETY REPORTING BY THE SPONSOR TO THE COMPETENT AUTHORITIES:

Serious adverse events (SAE) occurring during the clinical trial will be reported in compliance with all pertinent local and national regulations of the European countries participating in the study.

Cerus Endovascular and genae safety team are responsible for the assessment, evaluation and reporting of serious adverse events for the above-mentioned clinical trial. Safety reporting to the CA and ethics committee, responsibilities and timelines are detailed hereunder and will be done according to EN ISO 14155:2011, MEDDEV 2.7/3 revision 3 and national regulations (German MPSV).

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**Contact Details:**

Cerus Endovascular Inc.

47757 Fremont Blvd

Fremont, CA 94538

Tel: +1 510 364 5046

Email : carol.holt@cerusendo.com

**Germany**:

Reporting of SAEs will be undertaken according to Section 3 sub-section 6 of the Ordinance on Medical Devices Vigilance (MPSV).

The definition of SAE's will be in accordance with Section 2 number 5 of the MPSV which states:

"A serious adverse event is defined as any occurring undesired adverse event in a clinical study or performance evaluation study with subject to approval that led directly or indirectly to a death or to a serious deterioration in health either in subjects, users or other persons whether or not related to the investigational medical device".

All serious adverse events, regardless of country of occurrence, will be entered on to the MEDDEV 2.7/3 SAE report table and submitted to BfArM and other relevant Competent Authorities every quarter at a minimum. In addition, the following conditions will be adhered to:

- SAEs occurring in Germany where a causal relationship between the investigational medical device (Contour neurovascular system™) and/or the procedure cannot be excluded will be reported individually on a BfArM SAE Report form and sent to MPSAE@bfarm.de
  Such events will be reported immediately upon knowledge of the event. These events will subsequently be added in a cumulative manner to the summary table.
- SAEs meeting the above criteria occurring outside Germany will be added to the SAE summary MEDDEV table and reported immediately upon knowledge of the event to MPSAE@bfarm.de
- Where a causal relationship between the SAE and the investigational medical device or the procedure can be excluded will be consecutively added to the summary table and reported quarterly and sent to MPSAE@bfarm.de
- On a quarterly basis, an evaluation report of all SAEs will be provided to BfArM using the SAE summary evaluation template available on the BfArM website.
  http://www.bfarm.de/EN/Service/Formulare/medDev/mp-forms-startseite_en.html

2.2 SAE Reporting Flow

A Case Report Form (CRF) will be included on the Electronic Data Capture (EDC) platform to enable participating centers to register and report all events immediately upon knowledge. Events will be classified and assessed for regulatory reporting by Cerus Endovascular and the genae safety team. During causality assessment activity, clinical judgement shall be used and the relevant documents



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will be consulted. Events meeting the criteria for immediate reporting to Competent Authorities will trigger the completion of a SAE Report form or summary table which will be forwarded to BfArM as well as all other relevant Competent Authorities and Ethics Committees in the participating countries as required.

A Clinical Event Committee (CEC) will be established by Cerus Endovascular or designee to assess, review and classify all neurologic, device-related and procedure-related SAEs to ensure they are reported accurately. The CEC member(s) appointed for the study will be qualified by background, training and expertise in neurovascular treatment of intracranial aneurysms. The member(s) will not be an investigator on the study. The CEC will regularly review and adjudicate the adverse events and any deaths. Classification of the events will include device and procedure relatedness and seriousness. Member(s) will be provided data summaries and source documentation for review.

### 2.3 Data Safety Monitoring Board (DSMB)

A DSMB will convene of member(s) experienced in an associated discipline. The DSMB will review the study data after enrollment of the first five patients. Enrolment of further patients will occur as the DSMB reviews the data. The DSMB will provide a report following the review and advise Cerus Endovascular for any modifications or concerns that may be necessary. The DSMB will provide further evaluation at least twice per year and after the first 5 are enrolled. If slow enrollment is experienced, the DSMB may meet less frequently.

## 3. Protection of subjects and their data

### 3.1 Statement on vulnerable subjects

Individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by expectations, such as hospital and laboratory personnel or employees of the sponsor, will not be included in this clinical trial.

### 3.2 MPG §20 Art. 4 and 5 - Statement on minors and pregnant women

Minors (<18 years) or pregnant women will not be enrolled in this clinical trial.

### 3.3 MPG §21 Art. 2 – Statement on incapacitated subjects

This clinical study will not be performed on a person who is legally incapacitated or whose capacity is limited by contract.

### 3.4 Secure handling of subject data

For this clinical study only pseudonymized subject data will be captured, saved and used for any reporting or analysis purposes.

All documents, i.e. images or documents that contain subject identifiers will be pseudonymized prior to providing them to any party involved in the study.

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Identifiers that will be pseudonymized include: Subject name, initials, address, date of birth and any information which, in conjunction with other data held or disclosed to the recipient, might identify the subject.

Each study subject will have a unique identifier for which only the study site will hold "the key" to identify the subject's identity via their identification log. Any identification key(s) will not leave the study site.

Only pseudonymized data will be entered into a central electronic data capture (EDC) system, or database, namely into electronic case report forms (eCRFs), accessible by the study site, CRO and Sponsor. Subject name, initials, address and date of birth, or other identifying information will never be entered in this database.

Analysis and publication of the study may make it necessary to send the pseudonymized data to countries where an appropriate level of data protection is not ensured, for example to the US. However, these data will not contain any personal identification features and the Sponsor, Cerus Endovascular Inc., will make every effort to maintain confidentiality to the same extent as in the European Union.

## 4. Qualification of Investigators

### 4.1 Training on the Use of the Medical Device

The Sponsor and the site principal investigator will ensure that the Sub-Investigators handling the device will receive training and instructions on the use of the device being tested according to MPKPV §9 (2) N°1 prior to performing any study procedures. The device should only be used by physicians licensed and credentialed to perform endovascular embolization catheterization procedures. The sponsor will ensure that each investigator, who will be handling the Contour Neurovascular System™ through-out the trial, receives proper training on the device via flow models, didactic slide presentation and implant simulation using the replicator. This training will be provided the latest during the Site Initiation Visit and will be documented on a Site Training Log.

A patient selection committee will provide guidance over the identification of the first six patients at each site to facilitate successful patient identification and implantation. The patient selection committee will be formed of multiple implanting clinicians from around the world whom are trained and/or experienced with Contour and previous experience with embolization devices used in aneurysm treatment. The committee will have access to the patient images submitted by the investigator during the screening process. The selection committee will individually review and cast opinion on whether the proposed aneurysm is treatable with a Contour device. The primary purpose for the selection committee is to provide independent oversight for appropriate patient selection while also removing bias from patient selection (i.e. the sponsor will support the selection of cases according to the IFU, but the committee can provide clinical expertise toward the suitability of the specific anatomy of the patient and aneurysm.)



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Physician proctoring by a consulting clinician will occur for the first three implants at a newly implanting center. The proctor will provide feedback and guidance for the implantation of the Contour Neurovascular System™ after the selection committee determines the aneurysm is treatable. A sponsor representative will also be available for at least the initial six implantation procedures.

In the event that a Sub-Investigator could not attend the detailed device training during the Site Initiation Visit or if a new Sub-Investigator joins the study team, the Sponsor will ensure appropriate training on handling of the Contour Neurovascular System™ is provided and documented on a Site Training Log. If requested by the responsible Ethics Committee, training documentation can be notified.

### 4.2 Conduct of Trail according to German Law – MPG and MPKPV

The Investigator assures that the clinical trial will be conducted according to the clinical trial protocol and the legal regulations on the prerequisites for carrying out clinical trials in humans according to MPG and MPKPV.

The investigator must be familiar with the basic principles of medical product law, the legal and scientific bases of clinical trials or performance evaluation tests and the resulting obligations according to MPKPV § 9 (2) N°2.

The investigator declares that he/she has been instructed according to MPKPV § 9 (2) N°2 on the Clinical Investigation Plan (CIP), this CIP Addendum and the Investigator Brochure and in the resulting obligations.

The investigator confirms that in accordance with MPG § 20 (1) N°7 he/she has been informed about the results of the biological safety assessment and the examination of the technical safety as well as the risks presumably associated with this clinical trial.

## 5. Archiving

### 5.1 ARCHIVING REQUIREMENTS:

Archiving of the clinical trial documents will be conducted according to Directive 2005/28/EC Article 17-19 as well as national guidelines:

Cerus Endovascular Inc. will ensure that during the entire course of this clinical trial, all trial data will be protected against unauthorized access. In addition, the sponsor and investigators shall take all necessary measures for a careful and confidential handling of all clinical trial information.

For Germany: According to MPKPV § 10 (7) all data from the clinical investigation will be stored for a period of 10 years after the completion or termination of the trial.

# 19 APPENDIX D – Report of Prior Investigations

## 19.1 First-In-Human Clinical Study – Contour Compassionate Use

A total of 4 patients received the Contour implant under a Compassionate Use (expanded access) approval by the Clinica La Segrada Familia, Ethics Committee (EC). The rationale was that the Contour implant could potentially treat patients with difficult, complex, unruptured intracranial aneurysms (IA)s with less risk compared to other alternatives. The procedures were performed by neuro interventional radiologist, Pedro Lylyk, M.D., at Clinica La Sagrada Familia, Buenos Aires, Argentina.

The patient baseline demographics are shown in **Table 7**.

**Interim Results** (Update report is expected 31 July 2018)

All 4 patients (4/4, 100.0%) were Caucasian females. The mean age was 65.8 years (yrs) old.

**Table 7 FIM Study: Baseline Demographics**

| | **Gender** | **Age (yrs)** | **Ethnicity** |
|---|---|---|---|
| Patient 1 | Female | 65 | Caucasian |
| Patient 2 | Female | 75 | Caucasian |
| Patient 3 | Female | 58 | Caucasian |
| Patient 4 | Female | 65 | Caucasian |

Three out of 4 patients (3/4, 75.0%) had multiple IAs. One out of 4 patients (1/4, 25.0%) had a history of bilateral carotid stenosis that required stenting and percutaneous transluminal angioplasty (PTA). Two out of 4

patients (2/4, 50.0%) were on dual anti-platelet (DAP) therapy for prior implants (carotid stent and flow diverter) in the parent artery.

Detailed Clinical characteristics are shown in **Table 8** below:

**Table 8 Clinical Characteristics**

| | IA Location | Symptoms related to IA | Neuro exam findings | Medical History |
|---|---|---|---|---|
| Patient 1 | Anterior Communicating Artery (ACom) | None | Rotatory horizontal nystagmus | Arterial Hypertension<br><br>Dilated Cardiomyopathy<br><br>Right Middle Cerebral Artery (MCA) IA previously treated with Web device<br><br>Left pericollosal IA previously treated with coils |
| Patient 2 | Left MCA | None | Unable to evaluate neurologically | Ruptured, Right Posterior communicating Artery (PCom) previously treated with coils<br><br>Subarachnoid hemorrhage (SAH) secondary to ruptured PCom<br><br>Arterial Hypertension |
| Patient 3 | Hypophyseal | Headache (HA) | No abnormal findings | Right carotid ophthalmic previously treated with Pipeline Embolization device (PED) – patient placed on DAP medications |
| Patient 4 | Right MCA | None | No abnormal findings | Hypertension<br><br>Dyslipdemia<br><br>Bilateral carotid stenosis requiring stent placement - patient placed DAP medications |

Three out of 4 patients (3/4, 75.0%) have completed their 12 month follow-up visits. See **Table 9** for the details:

**Table 9 Procedure and Follow-Up Visit**

| | Procedure | 30 Day FU | 6 Month FU | 12 month FU |
|---|---|---|---|---|
| Patient 1 | Date: 2015-10-19<br>No Adverse Events (AE)s, Adverse Device effects (ADE)s or Device Malfunctions<br><br>Cerebral angiogram demonstrated immediate stasis of blood flow within IA after Contour was deployed | Remained asymptomatic; Normal neuro exam; No AEs<br><br>Cerebral angiogram demonstrated partial occlusion | Remained asymptomatic; Normal neuro exam; No AEs; No device migration<br><br>Cerebral angiogram demonstrated partial occlusion | Remained asymptomatic; Normal neuro exam; No AEs; |
| Patient 2 | Date: 2015-10-19<br>No AEs, ADEs or Device Malfunctions<br><br>Cerebral angiogram demonstrated immediate stasis of blood flow within IA after Contour was deployed | Cerebral angiogram demonstrated aneurysm is smaller in size compared to baseline | Patient has not returned for 6 month FU Patient deceased as a result of complications from initial stroke. SAE related to pre-existing condition. | N/A |
| Patient 3 | Date: 2015-10-20<br>No AEs, ADEs or Device Malfunctions<br><br>Cerebral angiogram demonstrated immediate stasis of blood flow within IA after Contour was deployed | Asymptomatic; Normal neuro exam; No AEs<br><br>Cerebral angiogram demonstrated decreased flow within the IA | Remained asymptomatic; Normal neuro exam; No AEs; No device migration<br><br>Cerebral angiogram demonstrated Contour in good position with partial occlusion | Remained asymptomatic; Normal neuro exam; No AEs;<br><br>Patient refused angiogram |

| | | | | |
|---|---|---|---|---|
| Patient 4 | Date: 2015-10-26<br>No intraprocedural Adverse Events (AE)s, Adverse Device effects (ADE)s or Device Malfunctions<br><br>Two days post-procedure, patient had a transient right pseudo femoral aneurysm confirmed via echodoppler. | Asymptomatic; Normal neuro exam; No AEs<br><br>Cerebral angiogram demonstrated decreased flow within the IA | Remained asymptomatic; Normal neuro exam; No AEs; No device migration<br><br>Cerebral angiogram demonstrated Contour in good position with partial occlusion | Remained asymptomatic; Normal neuro exam; No AEs; |
| | Physician rated it as mild in severity. No treatment was required for AE resolution. Physician rated it as related to the procedure but not the device.<br><br>Cerebral angiogram demonstrated immediate stasis of blood flow within IA after Contour was deployed | | | |

Overall, the Contour demonstrated an excellent safety profile with its initial clinical use on a complex set of patients.. There was 1 ADE in Patient #4 that was right femora pseudo aneurysm that resolved without treatment. It was rated as mild in severity by the PI. The second AE was a SAE in patient #2 who died as a result of a complication from a pre-existing condition. These AEs were anticipated and are similar to those expected for aneurysm embolisation procedures. The remaining 3 patients did not have any AEs at their 12 month follow-up visits.

In its initial clinical use, the Contour demonstrated an excellent safety profile in all 4 patients and performed as intended. The physician reported that there was 100% technical success with all 4 cases. Follow-up angiograms demonstrated partial occlusion of the IA.

## 19.2 Study INCA: Intracranial Aneurysm Treatment with NeXsys

The INCA study includes 3 patients that was conducted at La Clinica Sagrada Familia, Buenoe Aires in accordance with good clinical practices as described in ISO 14155:2011, with the Helsinki Declaration adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964, as amended by the World Medical Assembly, and under ethics committee approval and is approved by Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT).

### 19.2.1 Interim Results

The patient baseline demographics are shown below.

Two out of 3 patients were female (2/3, 66.6%). All 3 patients were Caucasian. The mean age was 67 yrs old.

Demographics

| | Gender | Age (yrs.) | Ethnicity |
|---|---|---|---|
| Patient 001JIM | Female | 77 | Caucasian |
| Patient 002-PEZ | Male | 62 | Caucasian |
| Patient 003-PAR | Female | 62 | Caucasian |

Clinical Characteristics

| | **IA Location** | **Symptoms related to IA** | **Neuro exam findings** | **Medical History** |
|---|---|---|---|---|
| Patient 001-JIM | Pericallosal | None | None | Non (never) Smoker<br>PComm aneurysm previously treated with coils |

| | | | | |
|---|---|---|---|---|
| Patient 002-PEZ | Rt. A1/2 | None | None | Current smoker<br>Existing Lt MCA bifurcation aneurysm and Lt Cavernous Carotid aneurysm under watchful waiting<br>Current history of Hypertension, Obesity, Dyslipidemia and Asthmatic<br>Current medication, Carvelidol and Valsartan for Hypertension and Estatin for Dyslipidemia<br>Pituitary Macroadenoma with previous Rt frontal craniotomy surgery.<br>Long standing bilateral visual field defects (Rt temporal hemianopsia and Lt Temporal quadrantopsia) |
| Patient 003-PAR | Rt. Carotid Bifurcation | Headache (HA) | None | Non (Never) smoker<br>No prior history aneurysm |
| | | | | Hypothyroidism currently on Levothyroxine |

## Procedure and Follow-Up Visits

| | Procedure | 30 Day FU | 6 Month FU |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Patient 001JIM | Date: 2016-May-09<br>11mm device deployed which failed to open fully. Device retrieved without incident and replaced with 9mm device<br>Peri procedural slight vasospasm distal to A1 to ACCA bifurcation cleared using 10mg diluted to 30% Nimodipine intra-arterially<br>Cerebral angiogram demonstrated slowed filling of the aneurysm with contrast media within IA after NeXsys was deployed | Remained asymptomatic; Normal neuro exam; No AEs<br>Device remained stable<br>Cerebral angiogram demonstrated partial reduction of flow into the IA with poor device apposition<br>AE: Patient remained hospitalized as a result of complications of SAH from ruptured Lt PComm aneurysm treated 6 days before NeXsys procedure. Patient developed Hyponatremia. Discharged 32 days after index procedure. | Remained asymptomatic; Normal neuro exam; No AEs;<br>Cerebral angiogram demonstrated migration of the device distally into the aneurysm sac with blood flow into the aneurysm |
| Patient 002-PEZ | Date: 2016-Jun-08<br>No AEs, ADEs or Device Malfunctions during the procedure or before discharge.<br>Cerebral angiogram demonstrated immediate stasis of blood flow within IA after Contour was deployed.<br>SAE 9 days post procedure, patient presented to emergency room with Lt. Hemiplegia. MRA showed distal thrombus formation in | Patient refused 30-day angiogram | Cerebral Angiography at 6 months demonstrated complete aneurysm occlusion |

| | | | |
|---|---|---|---|
| | the ACA probably secondary to thrombus formation on the NeXsys device detachment marker in the parent vessel. The thrombus was treated with intra-arterial antiplatelet infusion. Resolved with no sequelae and patient discharged.<br>Device stable at 11-day post implant imaging. | | |
| Patient 3 | Date: 2016-Sep-02<br>No AEs, ADEs<br>Device Malfunction of 9mm device where the implant did not fully open. Device retrieved and returned for inspection where it was found to have fibrin elements constricting the distal edge which had resulted in failure to fully open. New device opened and deployed without incident.<br>Cerebral angiogram demonstrated immediate stasis of blood flow within IA after NeXsys was deployed | Asymptomatic; Normal neuro exam; No AEs<br>Continues to be asymptomatic<br>Patient refused cerebral angiogram and MRI performed. | Cerebral Angiography at 3 months demonstrated complete aneurysm occlusion |

## Adverse Events

| Subject ID | Onset Date | Resolved Date | Event Description | SAE | Relation | Intervention, if Any |
|---|---|---|---|---|---|---|
| PEZ002 | 17 June 2016 | 20 June 2016 | Ischemic Stroke | Yes | Device Related | Patient underwent intra-arterial infusion of anti-platelet agent (Agrastat) under cerebral angiography and MRA follow up. Patient discharged without sequelae. |

| | | | | | | |
|---|---|---|---|---|---|---|
| JIM-001 | 13 May 2016 | 11 June 2016 | Hyponatremia | Yes | Not Device or Procedure Related | Sodium Chloride replenishment |
| JIM-001 | 13 May 2016 | 11 June 2016 | Urinary Tract Infection (UTI) | No | Not Device or Procedure Related | Antibiotics |

There was 1 AE that was a UTI that developed in Patient JIM-001 during their ICU stay that required antibiotics for resolution.

There was 1 ADE in Patient JIM-001 where the device was seen to have migrated into the aneurysm at 6month follow up. This device was not fully opposed to the aneurysm wall as seen on 3-month follow up.

In the patients enrolled to date, the Contour Neurovascular System™ continues to demonstrate a safety profile consistent with current practice. There were 2 SAEs, one related to the device which resulted in hemiparesis caused by thromboembolic complication. This resolved with the administration of intraarterial Agrestat and the patient was discharged with no sequelae on anti-platelet medication. A second SAE related to the patient's stay in the intensive care unit (ICU) where they developed Hyponatremia. This was resolved with sodium chloride replenishment and is related to the initial aneurysm rupture for which the patient was admitted.

## 19.3 European Pilot Clinical Study – Contour

A synopsis for the EU Pilot study is included below. The study includes 3 sites in the United Kingdom and one site in Hungary.

| | |
|---|---|
| **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<br>Specific AEs associated with this procedure that shall 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 embolize 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:<br>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 enrollment) |

## 19.4 Compassionate Use - Contour

The Contour Neurovascular System has been used under a compassionate use basis for 7 patients. The patients were implanted outside of the studies and have no prospectively defined data collection or analysis. To date, there have been 7 compassionate use implants worldwide for the Contour device, 4 in South America (see section 16.1), 2 in United Kingdom and 1in Denmark.

## 19.5 Compassionate Use - Neqstent

The Neqstent has been used under a compassionate/emergency use basis for 5 patients and all patients were in Denmark. The patients were implanted outside of the studies and have no prospectively defined data collection or analysis.

## 19.6 Summary of Animal Studies - Contour

This summary will provide an overview of the early animal and clinical research, as well as the laboratory testing conducted by Cerus Endovascular to evaluate the Contour Neurovascular System and Neqstentevaluate

### 19.6.1 Non-GLP Animal Studies

During the development phase of the Contour device, a series of non-GLP animal studies were performed to evaluate the usability, deployment, sizing and materials used in the initial prototypes. A total of 13 animals were evaluated in the first four animal protocols during development for these formative assessments of the device.

The final non-GLP animal study in 12 animals was conducted to evaluate the deployment, device stability when deployed across the neck of the aneurysm and the degree of exclusion of the aneurysm from circulation at 30 and 90 days post implantation. The protocol and reports associated with the nonGLP are included for your reference in Attachment 4.

### 19.6.2 GLP Animal Studies

A formal GLP Animal Study was conducted in preparation for human clinical trials. The study included treatment and analysis for 12 animals at 30- and 90-day time points. The protocol and final report are included for your reference in Attachment 5. A summary is provided below.

19.6.2.1 CONTOUR: GLP ANIMAL STUDY – CHRONIC FEASIBILITY STUDY SUMMARY

Report Document NPIMR CER277/15

Objectives

To assess the safety and efficacy of the Contour Neurovascular System™ to occlude blood flow in an experimental aneurysm animal model. Methods

The study was performed in compliance with the Good Laboratory Practice Regulations 1999 (S.I. No. 3106) as amended by the 2004 regulations (S.I. No. 994) which are based on the principles of Good

Laboratory Practice as adopted by the Organization for Economic Co-operation and Development (OECD), ENV/MC/CHEM (98) 17.

An induced experimental aneurysm model was used to investigate the Contour Neurovascular System™ as a treatment for intracranial aneurysm. The rabbit model has evolved over recent years as the species of choice for endovascular intracranial aneurysm due to three main factors:

- The rabbit model is similar to the coagulation system in humans.
- The dimensions of the extracranial carotid arteries are similar to the intra-arterial cerebral artery dimensions in the human.
- Elastase aneurysms in rabbits are similar in size and shape to those seen in humans.

Twelve male rabbits were used in the study, with six rabbits in the 30-day group and 6 rabbits in the 90day group. Group allocation was randomized. The study comprised of the following steps:

- The surgical creation of an aneurysm using the elastase model, targeting an aneurysm neck size between 3 and 6 mm.
- The placement of the test article in the aneurysm using fluoroscopic guidance.
- The assessment of performance of the test article using fluoroscopy, immediately after placement as well as at sacrifice 30 or 90 days later.
- The post-mortem harvest of test article with local vasculature for histology. The aneurysm neck was scored for platelet/fibrin thrombus, percent endothelialization, and neointimal formation, while the aneurysm sac was scored for sac organization, inflammation, and neoangiogenesis.

Main Outcome Measures

1. Test article detachment time, confirmed visually under angiography.
2. Test article positioning in the neck of the aneurysm, confirmed visually under angiography and by histology.
3. Test article stability *in situ* over 30 and 90 days, visually by angiography and by histology.
4. Evidence of aneurysm thrombosis following implant of the test article over 30 and 90 days, visually by angiography and by histology. Results

Twelve animals underwent device placement as per the protocol and angiographic results are available on 6 animals at 30 days and 6 animals at 90 days. All animals maintained healthy body weight throughout the duration of the study. Histology results are available on 5 animals at 30 days and 6 animals at 90 days. One aneurysm in the 30-day follow-up group was exceptionally small and did not withstand the preparation process for histology evaluation.

Safety results are as follows:

- The device was successfully deployed with 100% technical success in 12/12 cases with no evidence of adverse events confirmed fluoroscopically by the implanting physician. Histopathology at 30 and 90 days demonstrated no wall laceration or tears due to the implant.
- In 12/12 animals parent vessel flow was maintained with no evidence of thrombo-emboli.

- 12 of 12 devices detached within the design specification time of less than 120 seconds average and less than 180 seconds maximum.

Efficacy endpoints are as follows:

1. Stasis of blood flow in the aneurysm was achieved in all cases within 15 minutes with most aneurysms, demonstrating stasis immediately post detachment.
2. Intra-aneurysmal thrombus was assessed using both the angiography at follow-up (30/90 days) and histopathological assessment.

a. Angiography at 30 days: four grade 0 (complete occlusion), one grade 1 (90%+ occlusion), and one grade 2 (70-89% occlusion).

b. Angiography at 90 days: four grade 0 and two grade 1 (with minor flow at the neck of the aneurysm).

c. Histopathology at 30 days:

   i. Five of five aneurysms showed marked sac thrombus organization.

   ii. Four of five aneurysms showed marked neointimal growth across the neck. In one animal, the aneurysm was exceptionally small, and a portion of the device was positioned in the parent vessel. This device had a minimal amount of surface thrombus deposition on one side of the neck and had remained open to blood flow, not obstructing the parent artery.

d. Histopathology at 90 days:

   i. Six of six aneurysms showed marked sac thrombus organization.

   ii. Four of six aneurysms showed marked endothelial growth across the surface of the device and two of six showed moderate endothelial growth across the surface of the device.

   iii. Five of six aneurysms showed complete neointimal filling of the lumen.

e. 12 of 12 devices remained stable *in situ* during the follow-up time period. Conclusions

The animal study demonstrated excellent effectiveness and safety results with regards to the performance of the Contour Neurovascular System™ in the treatment of *elastase* aneurysms in the rabbit model. Specifically, endothelialization and neointimal coverage, combined with aneurysm occlusion was seen in all animals. No aneurysm or vessel perforations/damage and no device migration or movement were observed in the angiographic and histopathological analysis.

# 20 APPENDIX E – Case Report Form CRF Samples

| Cerus Endovascular<br>Clinical Study of the<br>Contour Neurovascular System™ **PATIENT ELIGIBILITY** | Site Number | | | Subject Number | | |
|---|---|---|---|---|---|---|
| | | | | | | |

| ***ENTRANCE CRITERIA*** | **Yes** | **No** |
|---|---|---|
| 1. Did subject meet all general entrance criteria | ☐ | ☐ |
| 2. Did subject meet all intra-procedural entrance criteria | ☐ | ☐ |
| 3. Date Informed Consent Signed | ☐☐ / ☐☐☐ / ☐☐ | |

*If Study Device placement was attempted, patient remains in the study.*

.

| ***PI SIGNATURE (IF SOURCE DOCUMENT)*** | | |
|---|---|---|
| **Name:** | **Date** (DD-MON-YY): | **Signature:** |
| | | |

| Cerus Endovascular<br>Clinical Study of the Contour Neurovascular System™<br>**DEMOGRAPHICS** | Site Number | | | Subject Number | | |
|---|---|---|---|---|---|---|
| | | | | | | |

| ***DEMOGRAPHICS*** | |
|---|---|
| 1. Birth Date | ☐☐/☐☐☐/☐☐ |
| 2. Gender | ☐ Male ☐ Female |
| 3. Ethnicity | N/A |
| 4. Race<br>*Check all that apply* | ☐ American Indian or Alaska Native<br>A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment<br>Asian<br>☐ A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent<br>Black<br>☐ A person having origins in any of the black racial groups of Africa<br>Native Hawaiian or Other Pacific Islander<br>☐ A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands<br>☐ White<br>A person having origins in any of the original peoples of<br>☐ Europe, the Middle East, or North Africa<br>☐ Unknown<br>Subject refused |
| ***VITAL SIGNS*** | |
| 5. Weight | ☐☐☐.☐ kg |
| 6. Height | ☐☐☐.☐ cm |

| | |
|---|---|
| 7. Blood Pressure | ☐☐☐ / ☐☐☐ mmHg |
| 8. Temperature | ☐☐ . ☐ ºC |
| 9. Pregnancy test result | ☐ Positive *(note: study exclusion)*<br>☐ Negative<br>☐ Not done<br>☐ Not applicable (male or postmenopausal woman) |

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Cerus Endovascular

Clinical Study of the
Contour Neurovascular System™

**DEMOGRAPHICS**

| Site Number | | | Subject Number | | |
|---|---|---|---|---|---|
| | | | | | |

| | | | |
|---|---|---|---|
| ***ANTI-THROMBOTIC MEDICATIONS*** | | | |
| 10. Total number of antiplatelet medications used pre-procedure | ☐☐ record any on medication log | | |
| 11. Total number of anticoagulation medications used pre-procedure | ☐☐ record any on medication log | | |
| ***MEDICAL HISTORY*** | | | |
| **Does patient have history of:** | | | |
| 12. Arrhythmia, non-Atrial Fibrillation | ☐ Yes | ☐ No | ☐ Unknown |
| 13. Atrial Fibrillation | ☐ Yes | ☐ No | ☐ Unknown |
| 14. Cardiovascular Disease (documented CAD, Valvular Disease, CHF) | ☐ Yes | ☐ No | ☐ Unknown |
| 15. Connective Tissue Disorder (i.e. systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis, dermatomyositis) | ☐ Yes | ☐ No | ☐ Unknown |
| 16. Diabetes Mellitus | ☐ Yes | ☐ No | ☐ Unknown |
| 17. Hyperlipidemia requiring medication | ☐ Yes | ☐ No | ☐ Unknown |
| 18. Peripheral Vascular Disease | ☐ Yes | ☐ No | ☐ Unknown |
| 19. Hypertension requiring medication | ☐ Yes | ☐ No | ☐ Unknown |
| 20. Renal Insufficiency (Creatinine > 2.5 mg/dL) | ☐ Yes | ☐ No | ☐ Unknown |

| | |
|---|---|
| 21. Smoking | ☐ Never smoked<br>☐ Current smoker<br>☐ Previous smoker |

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| Cerus Endovascular<br>Clinical Study of the Contour Neurovascular System™<br>**DEMOGRAPHICS** | Site Number | Subject Number |
|---|---|---|

| ***NEUROVASCULAR MEDICAL HISTORY*** | | | |
|---|---|---|---|
| 22. History of stroke | ☐ Yes | ☐ No | ☐ Unknown |
| 22.1 If Yes, date most recent stroke | ☐☐/☐☐☐/☐☐ | | |
| 22.2 If Yes, type of stroke(s) Ischemic<br>Intracranial Hemorrhage<br>Subarachnoid Hemorrhage | ☐<br>☐<br>☐ | *Check all that apply* | |
| 23. History of serious head trauma | ☐ Yes | ☐ No | ☐ Unknown |
| 24. History of Hydrocephalus | ☐ Yes | ☐ No | ☐ Unknown |
| 24.1 If Yes, date most recent Hydrocephalus | ☐☐/☐☐☐/☐☐ | | |
| 25. History of Seizure | ☐ Yes | ☐ No | ☐ Unknown |
| 25.1 If Yes, date most recent seizure | ☐☐/☐☐☐/☐☐ | | |
| 26. History of other cerebral aneurysm | ☐ Yes | ☐ No | ☐ Unknown |
| 26.1 If Yes, date most recent aneurysm | ☐☐/☐☐☐/☐☐ | | |
| ***SIGNS AND SYMPTOMS*** | | | |
| 27. Severe Headache | ☐ Yes | ☐ No | ☐ Unknown |
| 28. Proptosis or Exophthalmos | ☐ Yes | ☐ No | ☐ Unknown |

| | | | |
|---|---|---|---|
| 29. Conjunctival chemosis | ☐ Yes | ☐ No | ☐ Unknown |
| 30. Ocular bruit | ☐ Yes | ☐ No | ☐ Unknown |
| 31. Visual Loss | ☐ Yes | ☐ No | ☐ Unknown |
| 32. Epistaxis | ☐ Yes | ☐ No | ☐ Unknown |

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Cerus Endovascular

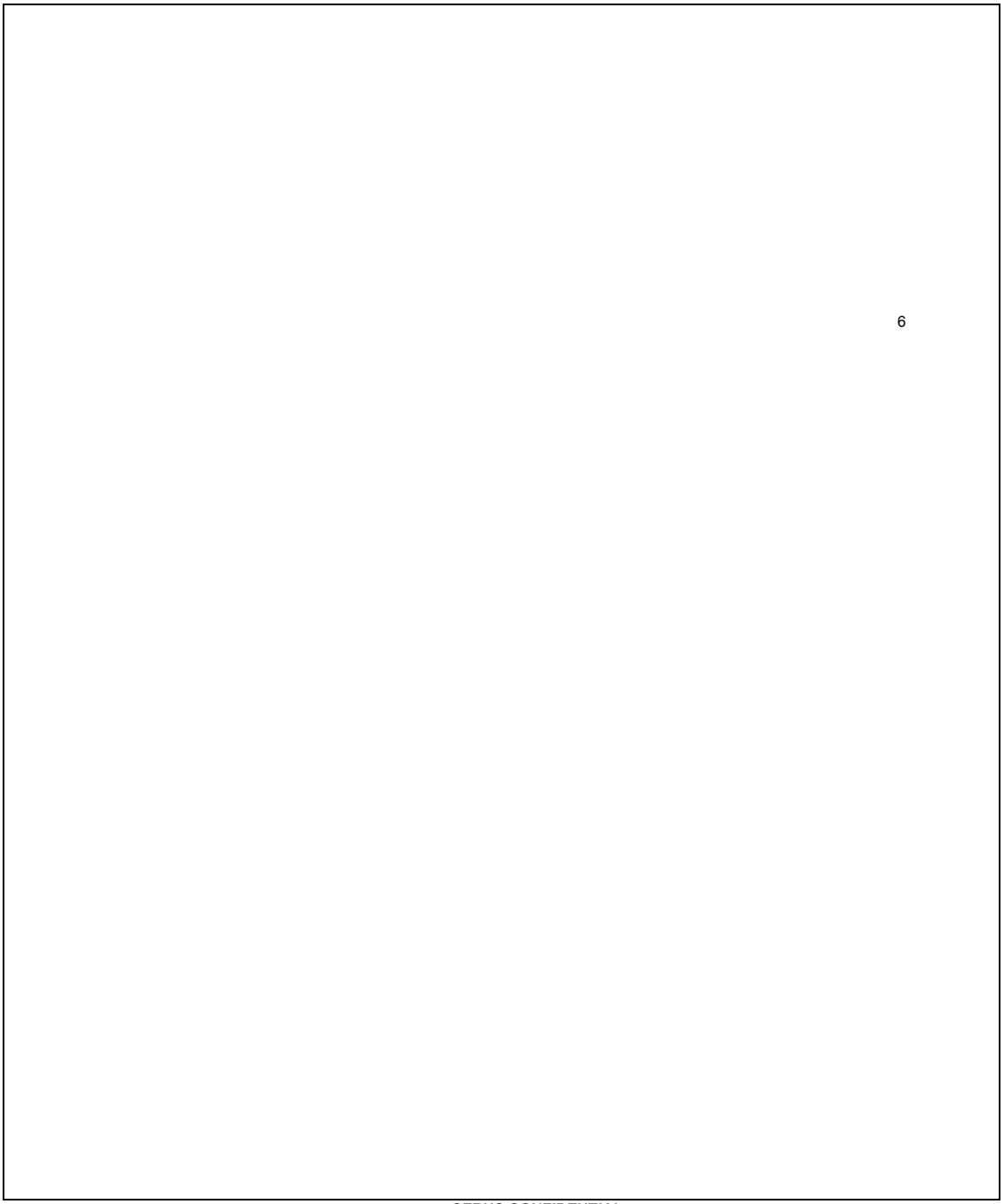
Clinical Study of the
Contour Neurovascular System™
**DEMOGRAPHICS**

| Site Number | | | Subject Number | | |
|---|---|---|---|---|---|
| | | | | | |

| ***CRANIAL NERVE PALSY*** | | | | |
|---|---|---|---|---|
| 33. Cranial Nerve Palsy | | ☐ Yes | ☐ No | ☐ Unknown |
| *If yes, Specify location:* | | | | |
| 1 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 2 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 3 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 4 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 5 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 6 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 7 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 8 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 9 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 10 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 11 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| 12 | ☐ Right Side | ☐ Left Side | ☐ Unknown | ☐ N/A |
| ***PREVIOUS NEUROVASCULAR PROCEDURES*** | | | | |
| 34. Carotid stent placement | | | ☐ Yes ☐ No | ☐ Unknown |
| 35. Carotid endarterectomy | | | ☐ Yes ☐ No | ☐ Unknown |
| 36. Prior treatment of aneurysm other than target | | | ☐ Yes ☐ No | ☐ Unknown |
| 36.1 Specify Treatment(s) | | | ☐ Intracranial coils<br>☐ Other device, specify: _____<br>☐ Other treatment, specify: _____ | |
| 36.2 Date of most recent procedure | | | ☐☐/☐☐☐/☐☐ | |
| 37. Other neurovascular procedure(s) | | | ☐ Yes ☐ No | ☐ Unknown |
| 37.1 Specify type of procedure(s) | | | 1) _____<br>2) _____<br>3) _____<br>4) _____<br>5) _____ | |
| 37.2 Date of most recent procedure | | | ☐☐/☐☐☐/☐☐ | |
| 38. Date target lesion discovered | | | ☐☐/☐☐☐/☐☐ | |

| Cerus Endovascular<br>Clinical Study of the Contour Neurovascular System™<br>**NEUROLOGICAL TESTING - BASELINE** | Site Numb ₃r | Subject Number |
|---|---|---|
| | | |

| | |
|---|---|
| ***GLASGOW COMA SCALE (GCS)*** | ☐ Not done |
| Exam Date | ☐☐/☐☐☐/☐☐ |
| Performed by | _____ |
| GCS Total Score | ☐☐ 3 - 15 |
| ***MODIFIED RANKIN SCALE (MRS)*** | ☐ Not done |
| Exam Date | ☐☐/☐☐☐/☐☐ |
| Performed by | _____ |
| mRS Grade | ☐ 0 - 6 |
| ***NIH STROKE SCALE (NIHSS)*** | ☐ Not done |
| Exam Date | ☐☐/☐☐☐/☐☐ |
| Performed by | _____ |
| NIHSS Total Score | ☐☐ 0 - 42 |
| Subject sedated for exam | ☐ Yes ☐ No |
| Subject intubated and paralyzed for exam | ☐ Yes ☐ No |



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Cerus Endovascular

Clinical Study of the
Contour Neurovascular System™

**BASELINE ANGIOGRAM**

| Site Number | | | Subject Number | | |
|---|---|---|---|---|---|
| | | | | | |

***BASELINE ANGIOGRAM*** ☐ Not Done

An angiogram of the target aneurysm and parent vessel must be performed within 3 months of Enrollment

1. Date of Angiogram ☐☐/☐☐☐/☐☐

2. Angiogram performed by _____

3. Target IA Type ☐ Sidewall ☐ Bifurcation or Terminal ☐ Other, specify: _____

4. Target IA Width ☐☐.☐ mm

5. Target IA Neck ☐☐.☐ mm

6. Target IA Height ☐☐.☐ mm

7. Evidence of ruptured IA ☐ Yes ☐ No

| | |
|---|---|
| 8. Location of aneurysm Anterior, | ☐ Petrous, Cavernous, Paraclinoid – right<br>☐ Anterior, Petrous, Cavernous, Paraclinoid – left<br>☐ Anterior, ICA terminus – right<br>☐ Anterior, ICA terminus – left<br>☐ Anterior, MCA – right<br>☐ Anterior, MCA – left, level: _____<br>☐ Anterior, ACA / AComm – right<br>☐ Anterior, ACA / AComm - left<br>☐ Anterior, ICA / PComm – right<br>☐ Anterior, ICA / PComm - left<br>☐ Posterior, Vertebral - right<br>☐ Posterior, Vertebral – left<br>☐ Posterior, Basilar Trunk<br>☐ Posterior, Basilar Tip<br>☐ Posterior, Basilar / PComm – right<br>☐ Posterior, Basilar / PComm – left<br>☐ Anterior, Other, location: _____<br>Posterior, Other, location: _____ |

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