Cerus Endovascular

Study Protocol and Statistical Analysis Plan

Document Title: Coil **A**ssisted **F**low D**i**version: A prospective, single arm, multi-center study to assess the safety and performance of Neqstent in adjunctive therapy (CAFI Study)

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Study Information

Protocol Name	**C**oil **A**ssisted **F**low D**i**version: A prospective, single arm, multi-center study to assess the safety and performance of Neqstent in adjunctive therapy (CAFI Study)
Protocol Number	DNQS428-01
Device Name	Neqstent
Manufacturer	**Cerus Endovascular, Ltd.** John Eccles House Oxford Science Park Oxford, OX4 4G United Kingdom
Core Lab	**Eppdata GmbH** Lokstedter Steindamm 18 22391 Hamburg, Germany
Web-Based Image System	**CIMAR** Cimar UK Ltd 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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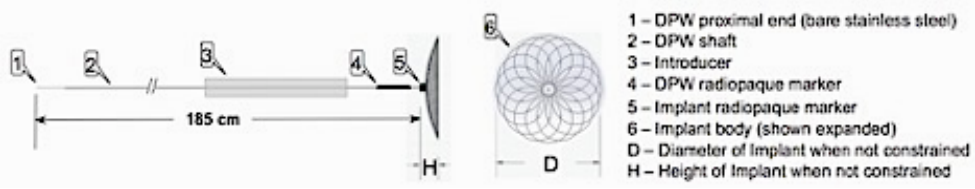
1 Overview

This document provides a detailed plan for Neqstent: **C**oil **A**ssisted **F**low D**i**version: A prospective, single arm, multi-center study to assess the safety and performance of Neqstent in adjunctive therapy (CAFI Study)

2 Clinical Study Synopsis

Study Title	**C**oil **A**ssisted **F**low D**i**version: A prospective, single arm, multi-center study to assess the safety and performance of Neqstent in adjunctive therapy (CAFI Study)
Study Purpose	Cerus Endovascular is sponsoring a prospective, single arm, multi-center study to document the safety and performance of Neqstent in adjunctive therapy. The purpose of the study is to document safety and performance of the Neqstent in adjunctive therapy in treatment for patients with intracranial aneurysms (IA).
Indications for Use and Intended Use	Neqstent is intended for use in conjunction with embolization coils for endovascular embolization of saccular 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 Neqstent before using the device.
Neqstent Training	Cerus Endovascular will provide training using flow models and didactic slide presentation. Physician proctoring will occur for the first three implants and an experienced Neqstent implanter 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 aneurysms or images will be viewed as forwarded by the treating physician.
Study Design	Prospective, single arm, multi-center study.

Study Size and Duration	**Study Size**: The study population will include 51 subjects enrolled and implanted at up to 11 centers. **Study Duration**: It is expected that the study will take 6 months to enroll a minimum of 51 patients. Follow-ups for the primary endpoint are the 6-month visit and 12-month visit, depending on the Raymond Roy score at the 6-month visit. Total duration of enrollment approximately 6 months, follow-up duration for primary endpoint (6-12 months), 24 months follow-up and reporting (3 months) will take approximately 33 months. 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. Any patient who is consented but has no implant attempt will be study exited.
Device Description	The Neqstent device works by providing a physical barrier between the parent vessel and the intracranial aneurysm neck (as demonstrated by the Neqstent clinical investigations as well as the pre-clinical research) thereby excluding the aneurysm from the parent artery blood flow. The Neqstent 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 - Neqstent The Neqstent (NQS) (NQS407-XX, NQS409-XX, NQS411-XX) is an intrasaccular, self-expanding, embolization device intended for the treatment of intracranial aneurysms. The NQS 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.

Device Description *(continued)*

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 fluoro-saver 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 Neqstent is offered in three sizes, suitable for embolization of intracranial aneurysm. Table 1 details the selection guideline for these three sizes:

The Neqstent 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 Neqstent only requires the neck 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)
NQS407-XX – 7 mm	3.0 - 5.0
NQS409-XX – 9 mm	4.0 - 6.0
NQS411-XX – 11 mm	5.0 - 8.0

[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

Objective and Endpoints	The primary objective of this study is to document the safety and performance of the Neqstent. **1. 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 ≥ 4 points and/or an increase from mRS baseline by >2. **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. Note: In the event of a Grade 2 or more using the Raymond Roy Scale, a second assessment will be made at 12 month follow-up to re-assess for remnant stability and/or complete occlusion and will be reported as a secondary efficacy endpoint.
Sample Size	51 subjects will be enrolled to obtain adequate follow-up data for the study to complete sponsor obligation to the notified body.
Number of Sites	Up to 11 sites will enroll in the study.
Study Visits	Baseline, procedure, discharge, one (1) month, six (6) months, twelve (12) months and twenty-four (24) months.

Enrollment and Eligibility	**Enrollment** 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 a Neqstent 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 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 Neqstent 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 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. • 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. 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.

Eligibility Criteria	Patients of all genders who meet all indications and contraindications will proceed to implantation. **Inclusion criteria** 1. Patient's indication for treatment of unruptured IAs according to the national/international guidelines. 2. Age 18-80 years at screening 3. Patients who are suitable for non-emergency endovascular embolization of saccular IAs 4. IA located at a bifurcation 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. Any patient anatomy, physiology, existing implants with failed aneurysm embolization that would interfere with the ability for Neqstent to seal at the neck of the aneurysm. (i.e., compacted coils in close proximity to the neck that prevent good apposition of the Neqstent to the wall of the aneurysm, stent and/or stent-like devices whose struts span the aneurysm neck to retain the coil mass that inhibit access and/or successful Neqstent seating at the aneurysm neck, and/or any aneurysm that has a failed device and confirmed thrombus-burden inside the aneurysm sac) 4. Contraindication for arterial access 5. Largest measured IA neck diameter >8 mm or ＜3 mm 6. Target IA contains other devices/implants (e.g., coils) that will prevent complete expansion of Neqstent 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 women of childbearing potential not on adequate birth control (only women with a highly effective method of contraception [oral contraception or intra-uterine device] or sterile women can be enrolled to the study) 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 18. The presence of condition that may create unacceptable risk during the aneurysm embolization procedure

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 (± 1 weeks)**	**6 months (± 1 month)**	**12 months (± 1 month)**	**24 months (± 1 month)**
Medical history and medications	X					X	
Neurologic Exam	X		X	X	X	X	X
NIH Stroke Scale	X	X*	X*	X*	X*	X	X*
Modified Rankin Scale (mRS)	X		X**	X**	X**	X**	X**
Medical history and medications	X					X	
Neurologic Exam	X		X	X	X	X	X
NIH Stroke Scale	X	X*	X*	X*	X*	X	X*
Modified Rankin Scale (mRS)	X		X**	X**	X**	X**	X**
Pregnancy test (pre-menopausal female)	X						
CT angiography (CTA) ^	X#				X	X****	
Magnetic Resonance Angiogram (MRA) ^	X#						
Cerebral Angiogram (DSA) ^	X# w/3D	X w/3D			X w/3D	X*** w/3D	
Adverse Event assessment		X	X	X	X	X	X
Procedure Information		X					
Aneurysm Occlusion Status – Raymond Roy and general assessment on study form##		X			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.

*** Cerebral angiogram is required at 6 months only; in the event of a Grade 2 or more using the Raymond Roy Scale at 6 months, a second cerebral angiogram assessment will be made at 12-month follow-up to re-assess for complete occlusion and will be reported as secondary efficacy.

**** CTA is required at 6 months only; in the event of a Grade 2 or more using the Raymond Roy Scale at 6 months, a second cerebral angiogram assessment will be made at 12-month follow-up to re-assess for complete occlusion and will be reported as secondary efficacy.

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

Background and Study Rationale	The most commonly provided endovascular therapy for intracranial aneurysms (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, aided by the water hammer effect, resulting in increased filling and re-growth of at the aneurysm from the neck. This creates a need for further intervention due to the lack of embolization of the aneurysm. Neqstent was designed to fulfill this clinical unmet need. Physicians' only course of available intervention is to continue to fill the aneurysm without the ability to seal and stabilize the wide neck. Neqstent is positioned at the neck of the aneurysm with the ability to leave in existing endovascular technology and also add more as needed to fully fill and close the aneurysm with the goal of complete occlusion or embolization. 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

[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.

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 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.

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 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, first generation device by the sponsor, is an intrasaccular 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 stable scaffold for the establishment of endothelial cells, across the neck and ultimately isolate the aneurysm from the parent artery blood flow. These two mechanisms of action may increase the likelihood of complete IA occlusion compared to embolization coils alone.

One intrasaccular flow diverter has received CE-mark and FDA approval. The WEB (Woven Endobridge Device, Sequent Medical, Terumo, Aliso Viejo, California) is a mesh device in a spherical shape. It works by mechanisms similar to Neqstent 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

[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.

[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

[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

	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 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] Contour 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. Neqstent is a derivative device and subject device for this study. It was designed as adjunctive therapy in patients where failed attempts at aneurysm embolization have occurred. Neqstent can be positioned at the neck of an aneurysm with existing coils and other embolization products. And, more adjunctive therapies can be added to fill the aneurysm after placement of Neqstent.

[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

[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

3 Acronyms

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

AE	Adverse event
ADE	Adverse device effect
CA	Competent Authority
CERUS	Contour Neurovascular System(TM) European Pre-Market Study
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	Ethics Committee
DSA	Digital Subtraction (Cerebral) 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
PMCF	Post market clinical follow-up
PI	Principal Investigator
SADE	Serious adverse device effect
SAE	Serious adverse event
SAH	Subarachnoid haemorrhage
SoC	Standard of Care
USADE	Unanticipated Serious Adverse Device Effect

4 Introduction

The Neqstent Implant is designed for endovascular treatment of intracranial aneurysms (IAs). The device is designed to be placed into the sac of an intracranial aneurysm through a standard endovascular procedure. Neqstent is a design derivative of the first generation Cerus intrasaccular Contour device implant. Neqstent is designed to be an adjunctive therapy to coil embolization which permits treatment of a broader range of aneurysm morphologies.

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 decreased 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. Multiple studies are available to estimate the relative increase in complete occlusion rate provided by these adjunctive devices. Even more challenging is the treatment of wide-necked IAs located at arterial bifurcations. Placement of intracranial stents in a variety of configurations has been associated with a significantly higher risk [6,7].

Incomplete occlusion has additional risks. Incomplete occlusion of IAs can lead to IA growth 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 cerebral angiography and retreatment. 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 placed either in the parent artery or in the IA itself. 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,[11] which can promote permanent occlusion of the target IA. These two components (flow disruption and scaffolding for re-endothelialization) 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.[12] 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.

Most flow diverting devices are placed into the parent artery; this requires the patient to take antiplatelet agents (aspirin and clopidogrel) for prolonged periods. The Neqstent device (Cerus Endovascular, Oxford, UK) is designed to be a flow diverter that is placed instead into the IA sac. Like other flow diverters, the device is designed to disrupt blood flow into the IA and to act as a scaffold upon which endothelial cells can grow. These two mechanisms of action may increase the likelihood of complete IA occlusion compared to embolization coils. Because the device is placed into the IA sac, antiplatelet therapy is not required. Use of antiplatelet and/or anticoagulation is at the discretion of the treating physician.

Neqstent is the design derivative flow diverting device manufactured by Cerus Endovascular. The Contour Neurovascular System™ ("Contour") is the first generation flow diverting device. The following are the differences between Contour and Neqstent:

Table 3. Contour and Neqstent Comparison

Features/Benefits	**Neqstent**	**Contour**	**Comments**
Simplified sizing approach taking only the aneurysm neck diameter into consideration when sizing	Yes	Yes	None
No parent artery stabilizing component unlike other adjunctive devices used in a coiling procedure. These benefits include; • eliminating the need to take the dimensions of the parent artery into consideration when sizing device • reduce or eliminate the need for anticoagulation therapy post procedurally.	Yes	Yes	None
Reduced risk of rupture since the device does not engage with the vulnerable aneurysm dome during the procedure	Yes	Yes	None
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	Yes	Yes	None
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	Yes	Yes	None
Improved durability of embolization by creating a stable scaffold across the aneurysm neck to permit establishment of stable endothelium.	Yes	Yes	None
Increased scaffold coverage across the neck permitting the physician to pack more coils without the risk of coil herniation or migration into the parent artery	Yes	No	Neqstent offers ability to be adjunctive therapy
Ability to retreat the more challenging failed or recurrent aneurysm which have previously been embolized and have left little room in the neck region to accommodate other adjunctive devices such as pCONUS or PulseRider. Additionally, branching vessels at the base of the aneurysm may be too small to accommodate parent vessel stenting or flow diversion to retreat aneurysms in these locations	Yes	No	Neqstent offers the ability for retreatment since it can be used adjunctively with coils/stents.

Features/Benefits	**Neqstent**	**Contour**	**Comments**
Ability for access by the coiling microcatheter either/both around or through the mesh of the implant giving the physician the flexibility to best embolize the aneurysm with the coiling microcatheter	Yes	No	Neqstent provides new way of closing aneurysm with the ability to use in conjunction with coils/stents.
Flow diversion from the implant can stabilize coil mass within the aneurysm sac and permit the establishment of thrombus	Yes	No	Neqstent can be used with coils/stents.

Other intrasaccular flow diverters are commercially available in Europe. As reviewed below, Sequent's WEB (Woven Endobridge) is a mesh device in a barrel shape. It works by mechanisms similar to Neqstent in that 1) it is a flow diverter, and 2) its mesh can serve as a scaffold upon which endothelial cells can grow. Published information regarding WEB is provided below.

Flow diverters have been commercially available since 2008. The first flow diverter was Pipeline Embolization Device (Covidien). A PubMed search for "Pipeline Embolization Device" on May 29, 2015 revealed 250 hits. A full summary of the Pipeline literature is beyond the scope of this review.

Many case reports of Pipeline use for large and giant or fusiform IAs have been reported (e.g., the first report in a giant fusiform IA[13]) but will not be summarized here. The device has been the subject of a number of large studies including:

- PITA, a prospective multicenter single-arm clinical trial of wide-necked or other difficult-to-treat or failed IAs.[14] The study showed a high rate of complete occlusion of the target IA with a good safety profile. The study enabled CE marking of the device.
- PUFS was a prospective, international multicenter single-arm clinical trial of large and giant IAs.[12] The trial showed a high rate of complete occlusion of the target IA and a good safety profile. The IAs in this study were particularly challenging and, in most cases, no other device was available to treat these IAs.
- INTREPED was a post-market retrospective assessment of use of this device in 793 patients in 17 centers worldwide.[15] The device was used in IAs throughout the brain arterial circulation. The neurologic morbidity and mortality rate was 8.4%. Subgroup analyses were used to examine predictors of adverse events. The target IA population was different (more complex) than the population proposed in the INCA study.

Other parent artery flow diverter devices are in clinical use, including FRED, LVIS (MicroVention Terumo), Surpass (Stryker), Silk (Balt), p64 (Phenox), Derivo (Acandis), and BRAVO (Cerenovus). All devices are made from metallic meshes similar to Neqstent. The published literature on these devices is less extensive compared to Pipeline Embolization Device but shows similar findings.

The published literature is very clear that flow diverters such as Pipeline Embolization Device, are now playing an increasing role in the treatment of wide-neck, large and giant, complex IAs. Their use in smaller IAs has been explored but is not accepted as standard treatment.

WEB (Woven Endobridge, Sequent Medical, Terumo, Aliso Viejo, California) is an intrasaccular flow diverter that shares characteristics with Neqstent and has both CE Mark and FDA approval. Because of the similarities, the published literature on WEB use is highly relevant.

- Ding[16] reported use of WEB in an animal study similar to those done to support Neqstent. The study showed complete occlusion in 33% of cases.
- Behme[17] reported a retrospective assessment of use of WEB in 52 patients (55 IAs), including 15 ruptured IAs. The device was deployed in all patients and implanted in 93%. Procedure complications occurred in 12%, including 2 thromboembolic events, 2 thrombus formations, 1 high-grade posterior cerebral artery stenosis, and 1 aneurysm rupture. None of these had clinical sequelae. Favorable angiographic results were seen in 29 (53%).
- Pierot[18] reported use of WEB in 21 IAs at 3 centers in the EU. All IAs were treated with the device and adjunctive treatment (coiling and/or stent placement) was used in 24% of patients. One patient (4.8%) has a symptomatic thrombotic event. Inadvertent detachment of WEB occurred in 1 patient. Complete occlusion of the target IA was seen in 7 (33%) IAs.
- Colla[19] reported use of WEB in 4 wide-necked basilar tip bifurcation IAs at a single Italian hospital. There were no perioperative adverse events and satisfactory occlusion was seen in all cases.
- Wallner[20] reported a patient treated with WEB who had IA recurrence requiring retreatment.
- Pierot[21] reported a prospective multicenter French study of use of WEB in 62 patients (63 IAs). Two versions of WEB were used. Morbidity was low (3.2% overall). Angiographic occlusion was not reported.
- Lubicz reported a multicenter experience with WEB use in 45 patients with 45 IAs treated with WEB.[22] Good clinical outcome was observed in 93%. Complete occlusion was observed in 30 (67%) patients in the short term (median 6 months) and 26 patients (58%) in the long term (median 13 months).
- Cognard[23] reported experience with WEB in 15 patients (15 IAs). Worsening of IA occlusion status was seen in 10 (67%) of cases, with compression of the implant. Complete occlusion at last follow-up was seen in only 1 case (6.7% of all patients).
- Papagiannaki[24] reported multicenter French retrospective WEB use to treat 83 patients with 85 IAs. Periprocedural complications were seen in 10.8%, with permanent neurologic deficits in 3.9%. Complete IA occlusion was seen in 37 (44%) of IAs at a median of 5.3 months of follow-up.
- Fiorella[25] reported interobserver agreement when judging IA occlusion with use of WEB. The degree of agreement was high.

The published literature on WEB is promising: it shows that intrasaccular flow diverters can be useful in a subset of IAs (primarily wide-necked IAs at arterial bifurcations). Periprocedural safety was good; complete occlusion of the target IA was often observed. However, compaction of the device may limit overall success rates.

In addition, there are also braided and laser-cut intra-arterial dwelling stents, such as, Solitaire AB (Medtronic), Enterprise 2, PulseRider (Cerenovus), LVIS Jr (Microvention Terumo), Baby LEO (Balt), ATLAS, Neuroform (Stryker), ACCLINO Flex Plus (Acandis) and pCONUS (Phenox). Substantial literature exists to support these various braided and laser-cut intra-arterial dwelling stents. Please see literature samples in **Table 4.** .

Table 4. Literature Samples

Title	Authors	Device(s)	Citation
Update on flow diverters for the endovascular management of cerebral aneurysms	Gary Rajah, MD, Sandra Narayanan, MD, and Leonardo Rangel-Castilla, MD	Various	Neurosurg Focus 42 (6):E2, 2017
How safe and effective are existing treatments for wide-necked bifurcation aneurysms? Literature- based objective performance criteria for safety and effectiveness	David Fiorella, Adam S Arthur, Richard Chiacchierini, Evelyne Emery, Andy Molyneux, Laurent Pierot	Various	Fiorella D, *et al*. *J NeuroIntervent Surg* 2017;**0**:1–5. doi:10.1136/neurintsurg-2017-013223
Endovascular techniques for the management of wide-neck intracranial bifurcation aneurysms: A critical review of the literature	Laurent Pierot, Alessandra Biondi	Various	Journal of Neuroradiology (2016) **43**, 167—175
Results of the ANSWER Trial Using the PulseRider for the Treatment of Broad-Necked, Bifurcation Aneurysms	Alejandro M. Spiotta, MD et al	PulseRider	Neurosurgery 00:1–10, 2017
The pCONUS device for the endovascular treatment of wide neck bifurcation aneurysms.	Lubicz B, Morais R, Alghamdi F, Mine B, Collignon L, Eker OF.	pCONUS	Lubicz B, et al. J Neurointerv Surg. 2016.
Coil occlusion of wide-neck bifurcation aneurysms assisted by a novel intra- to extra-aneurysmatic neck-bridging device (pCONUS): initial experience.	Aguilar-Pérez M, Kurre W, Fischer S, Bäzner H, Henkes H.	pCONUS	Aguilar-Pérez M, et al. AJNR Am J Neuroradiol. 2014.
Assisted coiling using LEO Baby or LVIS Jr stents: Report of six cases	Matías Negrotto, Roberto Crosa, and Walter Casagrande	Various	Interv Neuroradiol. 2015 Oct; 21(5): 566–574.
The LVIS/LVIS Jr. stents in the treatment of wide-neck intracranial aneurysms: multicentre registry.	Poncyljusz W, Biliński P, Safranow K, Baron J, Zbroszczyk M, Jaworski M, Bereza S, Burke TH.	LVIS	J Neurointerv Surg. 2015 Jul;7(7):524-9. doi: 10.1136/neurintsurg-2014-011229. Epub 2014 May 14.
Y-Stent-Assisted Coiling of Wide-Neck Bifurcation Intracranial Aneurysms: A Meta-Analysis.	Cagnazzo F, Limbucci N, Nappini S, Renieri L, Rosi A, Laiso A, Tiziano di Carlo D, Perrini P, Mangiafico S	Meta-analysis	Cagnazzo F, et al. AJNR Am J Neuroradiol. 2018.

Title	Authors	Device(s)	Citation
The Use of Solitaire AB Stents in Coil Embolization of Wide-Necked Cerebral Aneurysms	Teng-Fei Li et al	Solitaire AB	PLoS One. 2015; 10(10): e0139714
Safety and Efficacy of Low-Profile, Self-Expandable Stents for Treatment of Intracranial Aneurysms: Initial and Midterm Results - A Systematic Review and Meta-Analysis	Park S.-Y et al	Meta-analysis	Intervent Neurol 2017;6:170-182

In summary, parent artery flow diverters and stents are a widely accepted therapy options for treating wide-necked, large and giant IAs. Intrasaccular flow diverters are promising but present some difficulties in terms of placement and IA recurrence. Fiorella[25] concluded that "conventional therapies for WNBAs are associated with relatively low rates of complete occlusion and peri-procedural complications are not uncommon. Newer therapies are needed for the treatment of these aneurysms." Neqstent is an alternative to WEB that might be easier to place and, due to its design, result in better long-term angiographic outcomes.

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 Neqstent is comprised of the Neqstent implant (hereafter called "Neqstent"), which is pre-attached to a detachable pusher wire (DPW), and an Introducer. The DPW facilitates the delivery of the Neqstent 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 Neqstent 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 pre-attached DPW has a composite stainless steel and polymer construction. The Introducer is a single lumen polymer tube that is used to constrain the Neqstent implant during introduction into the MC hub. The Neqstent implant body and proximal marker can be visualized under fluoroscopy.

Given the platinum core of the device's mesh and the platinum marker, the Neqstent 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 Neqstent 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.

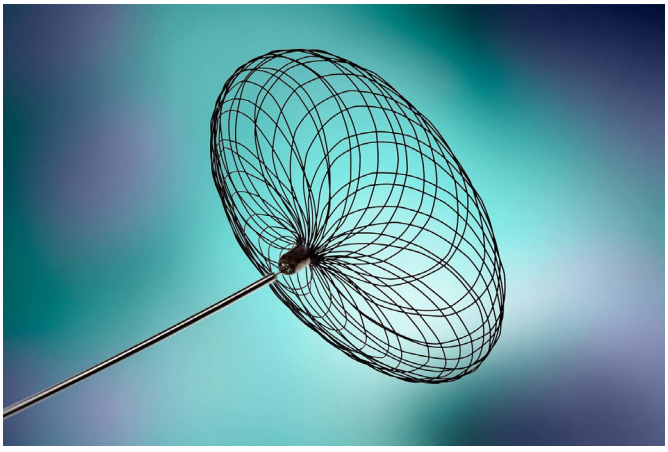


Figure 2. Neqstent Implant

5.2 Indications for Use and Intended Use

Neqstent is intended for use in conjunction with embolization coils for endovascular embolization of saccular 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 Neqstent before using the device.

The Neqstent is placed across the neck of the aneurysm to offer flow diversion as well as wire scaffolds spanning the neck of the aneurysm to support the retaintion of the coil mass inside the aneurysm sac. The device mesh also provides support for the establishment of neointimal cells across the aneurysm neck opening, providing long term stability of the neck and isolation of the aneurysm sac from the parent artery blood flow.

5.3 Training

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

- flow models
- didactic slide presentation

At least one patient selection committee will have access to the patient aneurysm images submitted by the treating physician during the screening process. The patient selection committee will individually review and cast opinion on whether the proposed aneurysm is treatable with a Neqstent device per product specification guidelines. Either a web-based image system called CIMAR will be used to view and store images along with the patient selection committee's opinion on aneurysm suitability for treatment based on the Neqstent sizing guidelines or images will be viewed as forwarded by the treating physician.

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 Neqstent after the patient selection committee has deemed 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 Neqstent 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 Neqstent has been performed. This assessment focused 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 Neqstent 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.

Table 5. Risks of Endovascular Aneurysm Treatment

Anticipated Risk	**Percent Anticipated Risk Occurrence**	**Specified Risks**
Neurovascular procedure related	Rarely (< 5%)	CVA – ischemic
	Rarely (< 5%)	CVA – hemorrhagic
	Rarely (< 5%)	Aneurysm rupture
	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

Anticipated Risk	**Percent Anticipated Risk Occurrence**	**Specified Risks**
	Rarely (< 5%)	Intra-cranial hypertension
	Less Likely (5-15%)	Recanalization of the aneurysm
Vascular Access Site procedure related	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
Assessment (SoC) related procedure: Angiogram	Less Likely (5-15%)	Allergic reaction to contrast media and Renal dysfunction secondary to contrast media. 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 child-bearing 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.
Other Risks related to general anesthesia and medication therapy	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.

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. Neqstent is being designed and developed in accordance with a risk management process that conforms with EN ISO 14971:2012. This process serves to identify hazards associated with the subject devices and accessories, estimate and evaluate the risks associated with those hazards, control (reduce) those risks, and monitor the effectiveness of that control. Risk management ensures that risks to the patient, users and third parties are minimized and determined to be acceptable. The risk management results are crosschecked against applicable risk reduction documentation to ensure the risk reduction measures are implemented.

The Cerus Endovascular design review process ensures that all identified risk reduction measures have been implemented. Residual risks, the risks remaining after risk control (i.e. risk reduction) measures have been taken, are addressed in the "Contraindications" and "Adverse Events" sections of the Instructions For Use as well as listed in Table 5.

Potential adverse events associated with use of Neqstent, some of which could be fatal or cause severe neurologic deficits, include:

- Aneurysm rupture causing intracranial hemorrhage
- Injury to parent artery causing thrombosis or hemorrhage
- Distal embolization of particles or blood clot causing stroke
- Parent artery vasospasm
- Parent artery dissection
- Aneurysm recanalization
- Infection
- Device migration causing incomplete occlusion, hemorrhage or ischemic stroke

Contraindications:

- Allergy to platinum, nickel or titanium

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 Neqstent. This study allows the Sponsor and Investigators to help other patients indicated for similar procedures

The Neqstent device is designed with materials and processes commonly used in medical devices used for IA treatment. The device is designed for easy placement and to increase the likelihood of

complete IA occlusion. Complete IA occlusion may reduce the risk of subsequent IA rupture, recanalization and requirement for retreatment.

As previously described, recent results from the use of existing intra-saccular flow disruptor devices have shown a risk of compression and compaction into the dome of the aneurysm and in instances significant neck regrowth. The Neqstent device is designed to seat across the neck of the aneurysm and delivery of embolic agents such as coils into the aneurysm sac. The stable framework of mesh across the neck will permit the physician to confidently pack more coils into the sac and the flow diverting properties will contribute to more stable healing. This may reduce the risk of subsequent IA recurrence or rupture or necessity for re-intervention.

In addition, potential benefits that may be associated with endovascular treatment instead of surgical intervention 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 Neqstent vs. standard endovascular aneurysm coiling:

- Simplified sizing approach taking only the aneurysm neck diameter into consideration when sizing
- No parent artery stabilizing component with the Neqstent device, unlike other adjunctive devices used in a coiling procedure. These benefits include:
  - eliminating the need to take the dimensions of the parent artery into consideration when sizing Neqstent
  - reduce or eliminate the need for anticoagulation therapy post procedurally.
- Reduced risk of rupture since the device does not engage 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
- Improved durability of embolization by creating a stable scaffold across the aneurysm neck to permit establishment of a stable endothelium layer
- Increased scaffold coverage across the neck permitting the physician to pack more coils without the risk of coil herniation or migration into the parent artery

- Ability to retreat the more challenging failed or recurrent aneurysm which have previously been embolized and have left little room in the neck region to accommodate other adjunctive devices such as pCONUS or PulseRider. Additionally, branching vessels at the base of the aneurysm may be too small to accommodate parent vessel stenting or flow diversion to retreat aneurysms in these locations
- Ability for access by the coiling microcatheter either/both around or through the mesh of the Neqstent giving the physician the flexibility to best embolize the aneurysm with the coiling microcatheter
- Flow diversion contribution from the Neqstent will stabilize coil mass within the aneurysm sac and permit the establishment of thrombus

6.3 Risk-to-Benefit Rationale

Neqstent has been implanted in compassionate use patients and is designed to be used adjunctively with embolization coils. The Neqstent device is an iteration of the Contour technology, which is the first-generation device, Contour, manufactured by the sponsor. Contour has been implanted in compassionate use patients, pilot study patients and pre-market clinical investigation CERUS 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 Neqstent demonstrate that when used under the conditions intended, the benefits associated with the use of the Neqstent 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 Neqstent.

7.3 Target Patient Population

The target patient population is patients with intracranial aneurysms 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. 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 as listed in Table 6.

Table 6. Eligibility Criteria

Inclusion Criteria	**Exclusion Criteria**
Patients of all genders who meet all indications and contraindications will proceed to implantation. 1. Patient's indication for treatment of unruptured IA according to the national/international guidelines. 2. Age 18-80 years at screening 3. Patients who are suitable for non-emergency endovascular embolization of saccular IAs 4. IA located at a bifurcation 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.	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. Any patient anatomy, physiology, existing implants with failed aneurysm embolization that would interfere with the ability for Neqstent to seal at the neck of the aneurysm. (i.e., compacted coils in close proximity to the neck that prevent good apposition of the Neqstent to the wall of the aneurysm, stent and/or stent-like devices whose struts span the aneurysm neck to retain the coil mass that inhibit access and/or successful Neqstent seating at the aneurysm neck, and/or any aneurysm that has a failed device and confirmed thrombus-burden inside the aneurysm sac) 4. Contraindication for arterial access 5. Largest measured IA neck diameter >8 mm or <3 mm 6. Target IA contains other devices/implants (e.g., coils) that will prevent complete expansion of Neqstent 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 women of childbearing potential not on adequate birth control (only women with a highly effective method of contraception [oral contraception or intra-uterine device] or sterile women can be enrolled to the study) 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 18. The presence of condition that may create unacceptable risk during the aneurysm embolization procedure

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 Neqstent 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 Neqstent 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 Neqstent implant along with coordinating aneurysm dimensions and definitions are provided in Table 7.

Table 7. Neqstent Sizes

REF (Catalog Number) – Diameter	Aneurysm Neck (mm)
NQS407 – 7 mm	3.0 - 5.0
NQS409 – 9 mm	4.0 - 6.0
NQS411– 11 mm	5.0 - 8.0

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 Neqstent. The Neqstent procedure may be scheduled following confirmation from the patient selection 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 Neqstent 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 and at 12 months if performed due to lack of complete occlusion 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 anesthesia.

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. These images will be the baseline submitted to the independent core laboratory for future comparisons at 6 months and 12 months.

7.7.4 Neqstent Procedure

Neqstent 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 Neqstent device is introduced into the microcatheter and slowly delivered into the target IA. The device is deployed at the neck of the aneurysm after the coiling microcatheter tip is inside the aneurysm sac, which would result in the microcatheter being jailed between the aneurysm wall and the Neqstent or the Neqstent is deployed prior to the introduction of the coiling microcatheter where the operator will navigate the coiling microcatheter through the mesh of the Neqstent to gain access to the aneurysm sac.

The Neqstent remains attached to the delivery wire throughout the entire embolization procedure and detachment or the device is the final step in the procedure once the physician has embolized the aneurysm sac with coils.

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 and occlusion 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, 12 months and 24 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 and 12 months (if the Raymond Roy scale is Grade 2 or higher 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 following the image transfer protocol. 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 8.

Table 8. Schedule of Assessments

	Baseline[#]	**Procedure**	**Discharge**	**1-month (± 1 weeks)**	**6 months (± 1 month)**	**12 months (± 1 month)**	**24 months (± 1 month)**
Medical history and medications	X					X	
Neurologic Exam	X		X	X	X	X	X
NIH Stroke Scale	X	X*	X*	X*	X*	X	X*
Modified Rankin Scale (mRS)	X		X**	X**	X**	X**	X**
Pregnancy test (pre-menopausal female)	X						
CT angiography (CTA) ^	X#				X	X****	
Magnetic Resonance Angiogram (MRA) ^	X#						
Cerebral Angiogram (DSA) ^	X# w/3D	X w/3D			X w/3D	X*** w/3D	
Adverse Event assessment		X	X	X	X	X	X
Procedure Information		X					
Aneurysm Occlusion Status – Raymond Roy and general assessment on study form##		X			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.

*** Cerebral angiogram is required at 6 months only; in the event of a Grade 2 or more using the Raymond Roy Scale at 6 months, a second cerebral angiogram assessment will be made at 12-month follow-up to re-assess for complete occlusion and will be reported as secondary efficacy.

**** CTA is required at 6 months only; in the event of a Grade 2 or more using the Raymond Roy Scale at 6 months, a second cerebral angiogram assessment will be made at 12-month follow-up to re-assess for complete occlusion and will be reported as secondary efficacy.

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 24 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 24 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 9. All AEs and device deficiencies shall be reported by the clinical site investigator on a specific case report form (CRF).

Table 9. AE Definitions per ISO 14155:2011

Adverse Event (AE)	An AE is: 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. Note 1: This definition includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse device effect (ADE)	An ADE is: an 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 o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolongation hospitalization, or o medical or surgical intervention to prevent life-threatening illness or o 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: an 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 follows.

- **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 10. AE Categorization

AEs	**Non-Device-Related**	**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

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 combined CEC/DSMB Committee 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 discipline. 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 is a group of physicians who are trained and experienced users of Neqstent/Contour who have previous experience with embolization devices used in aneurysm treatment. The patient selection committee will have access to the patient images submitted by the investigator during the screening process. The patient selection committee will individually review and cast opinion on whether the proposed aneurysm is treatable with a Neqstent device per product specification guidelines. The web-based image system called CIMAR will be used to view and store images and patient selection committee's opinion on aneurysm suitability for treatment based on the Neqstent sizing guidelines or images will be viewed as forwarded by the treating physician. A minimum of two physician votes will be obtained and a third in the case of a tie.

10 Statistical Analysis

This study intends to examine the safety and performance of the Neqstent used for the treatment for embolization of intracranial aneurysms. 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.

10.1 Justification of Methodology

This study is designed as a single arm, descriptive study to develop further understanding of the Neqstent. It will provide safety and performance information for subjects from the Neqstent implantation to 24-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. Note: In the

event of a Grade 2 or more using the Raymond Roy Scale, a second assessment will be made at 12- month follow-up to re-assess for complete occlusion and will be reported as a secondary efficacy.

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 Multi-center Trial Considerations

Up to 11 sites will participate in the study.

This is non-randomized, single arm, multi-center clinical study to assess safety and performance of Neqstent device with standardization of subject enrollment, data entry and AE reporting.

10.4 Endpoints

10.4.1 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 ≥ 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.

Note: In the event of a Grade 2 or more using the Raymond Roy Scale, a second assessment will be made at 12 month follow-up to re-assess for remnant stability or complete occlusion and will be reported as a secondary efficacy endpoint.

10.4.2 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.

10.5 Interim Analysis

The sponsor will submit an interim analysis summary of the clinical study's progress (on safety evaluation and device success) to the involved Ethics Committees and Regulatory Authorities after 10 patients are enrolled in the study.

Based on the results following the interim analysis summary, the sample size will be re-evaluated.

10.6 Sample Size Rationale and Statistical Considerations

This is a single arm study designed to provide adequate data for the purpose of a pre-market study. It is expected the 51 patients with evaluable data at 6 month and 12 month follow-up (where necessary) will show adequate evidence of safety and performance of Neqstent device.

For the purpose of sample size calculation, the primary outcome measurement is assumed to be the composite of the listed primary endpoint components.

Extensive literature search was conducted to gather information on the non-inferiority margin. Due to limited results found in literature, the non-inferiority margin for this study, $\delta = 10\%$, was chosen to align with the study design.

The sample size estimation was based on the following assumption:

- Success rate of the investigational is expected to be 70%
- Success rate of standard treatment is estimated to be 55%
- Power is set at 80% and one-sided significance level is set at 5%
- Expected rate of attrition is 10%

Based on the assumptions, a total of 46 subjects are required to show that the expected success rate of 70% is different than the true rate of 55% with a delta of 10%. Adding in additional subjects for anticipated loss to follow-up, 51 subjects are needed to be enrolled for a total of 46 subjects with 6 month data.

Analysis Population

The safety population consists of all patients who are implanted with the study device. The primary analysis for all safety endpoints will be performed on this population.

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.

Endpoint Analysis:

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 follow-up. In the event of a Grade 2 or more using the Raymond Roy Scale, a second assessment will be made at 12- month follow-up to re-assess for complete occlusion and will be reported as a secondary efficacy.

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.).

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 regularly 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 Neqstent 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

It is expected that the study will take 6 months to enroll a minimum of 51 patients. Follow-ups for the primary endpoint are the 6-month visit and 12-month visit, depending on the Raymond Roy score at the 6-month visit. Total duration of enrollment (6 months), follow-up duration for primary endpoint (6-12 months), 24 months follow-up and reporting (3 months) will take approximately 33 months.

Any patient who is consented but has no implant attempt will be study exited.

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/favorable 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

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

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
- 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 per EC guidelines
- 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.

The database will include built in edit checks which will facilitate data cleaning by identifying missing, illogical or inconsistent data at the time of entry. Monitors or other data reviewers may also enter manual queries to request additional data clarifications. Queries will be managed within the EDC as per Data Management Plan (document DNQS428-06) herewith enclosed in APPENDIX-E.

The Data-Management Plan will be developed to describe:

a) Procedures used for data review, database cleaning, and issuing and resolving data queries

b) Procedures for verification, validation and securing of electronic clinical data systems

c) Procedures for data retention

d) Specified retention period

e) Other aspects of clinical quality assurance, as appropriate

Electronic CRF Form samples are in APPENDIX F – Case Report Form CRF .

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 has fulfilled the data requirements. The sponsor will provide the report to the EC and regulatory authorities as required, as well as to the notified body.

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 and/or sponsor delegate 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 study 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 center 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) 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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2. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002;360(9342):1267–74.

3. Molyneux AJ, Birks J, Clarke A, Sneade M, Kerr RSC. 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). Lancet 2015;385(9969):691–7.

4. Johnston SC, Dowd CF, Higashida RT, et al. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rerupture After Treatment (CARAT) study. Stroke J Cereb Circ 2008;39(1):120–5.

5. Molyneux AJ, Clarke A, Sneade M, et al. Cerecyte coil trial: angiographic outcomes of a prospective randomized trial comparing endovascular coiling of cerebral aneurysms with either cerecyte or bare platinum coils. Stroke J Cereb Circ 2012;43(10):2544–50.

6. Ko JK, Han IH, Cho WH, et al. Crossing Y-stent technique with dual open-cell stents for coiling of wide-necked bifurcation aneurysms. Clin Neurol Neurosurg 2015;132:54–60.

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8. Kallmes DF, Ding YH, Dai D, Kadirvel R, Lewis DA, Cloft HJ. A second-generation, endoluminal, flow-disrupting device for treatment of saccular aneurysms. AJNR Am J Neuroradiol 2009;30(6):1153–8.

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10. Cognard C, Januel AC, Remnants and recurrences after the use of the WEB intrasaccular device in large-neck bifurcation aneurysms. Neurosurgery. 2015 May; 76(5):522-30; discussion 530. doi: 10.1227/NEU.0000000000000669.

11. Pierot L, Costalat V, Moret J, et al. Safety and efficacy of aneurysm treatment with WEB: results of the WEBCAST study. J Neurosurg. 2015 Sep 18:1-7. [Epub ahead of print]

12. ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice.

13. Directive for Medical Devices (MDD): 93/42/EEC and Active Implantable Medical Devices (AIMD) 90/385/EEC. Amended by Directive 2007/47 EC (European Council).

14. Article 2.3.5 under Clinical Evaluation (Annex VII, 90/385/EEC and Annex X 93/42/EEC).

15. MEDDEV 2.7/3 (2015) Guidelines: SAEs Reporting-Clinical Investigations.

16. MEDDEV 2.12-1 rev7 (2012): Guidelines on a Medical Devices Vigilance System.

17. MEDDEV 2.12-2 rev2 (2012): Guidelines on a Medical Devices, Post Market Clinical Follow-Up Studies.

18. WMA Declaration of Helsinki. Ethical Principles of Medical Research Involving Human Subjects. JAMA. 2013 Vol. 310 (20): 2191-2194.

19. MEDDEV 2.7.1 rev3 (2009): Clinical evaluation. A guide for manufacturers and notified bodies.

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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
A	0465	Initial Release	22 Feb 2019
B	0470	• Revise the number of patients from 35 to 50 • Revise the number of sites from 10 to 11 and remove site patient maximum • Remove secondary endpoints • Minor clarifications and corrections	22 Mar 2019
C	0497	1. The date and Rev in the header; 2. Updated title throughout CIP; 3. Clarified Study Purpose throughout; 4. Updated study size FROM: 10, TO: 11 centers, and follow up durations FROM: 12/21 months, TO: 24/33 months; 5. Removed 'and equatorial' from Device Description ; 6. Added Study Visit at 24 months throughout; 7. Inclusion criteria updated to specify "unruptured" IAs.; 8. The following inclusion criterion added: Patients who are suitable for non-emergency endovascular embolization of saccular IAs; 9. The following exclusion criterion added: Ruptured aneurysm; 10. The following exclusion criteria clarified: Pregnant, breastfeeding or planning pregnancy in the next 2 years changed to: Pregnant, breastfeeding or women of childbearing potential not on adequate birth control (only women with a highly effective method of contraception [oral contraception or intra-uterine device] or sterile women can be enrolled to the study); 11. The following exclusion criterion added: The presence of condition that may create unacceptable risk during the aneurysm embolization procedure; 12. Clarified 12 month follow up require mRS; 13. Clarified Justification Methodology; 14. Removed General Principles; 15. Clarified Multi-center Trial Considerations; 16. Revised Sample Size Rationale; 17. Clarified Recording Data on Electronic CRFs; 18. Updated Human Use for Neqstent and Contour data Tables (Sections 19.1 and 19.2); and 19. Clarified REF nomenclature from NQS## to NQS4##-XX.	16 Jul 2019
D	0525	1. Updated title throughout CIP to add "in adjunctive therapy" 2. Update number of patients to 51 where appropriate 3. Updated risk section 6.1 4. Added section 10.5.: Interim Analysis 5. Update section 10.6 : Sample Size Rationale and Statistical Considerations including enrollment of 51 subjects to yield 46 subjects with evaluable data	27 Sep 2019
D	0541	Correction Only: correct "four" to "three" on page 7	31 Oct 2019
E	0548	1. Update the Core Lab contact info 2. Exclusion criteria #6 clarified to be consistent with #3 (admin error)	14 Nov 2019
E	0564	Correction Only: In Study size and duration, remove "in Europe"	10 Dec 2019
F	0573	In §10.5, remove "Only after approval following the review of the interim analysis summary from Ethics Committees and Regulatory Authorities, further patient enrollment will be continued."	15 Jan 2020

16 APPENDIX A - Statement of Compliance and Signature Page

Clinical Investigation Number: DNQS428-01

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

Study Title: **C**oil **A**ssisted **F**low D**i**version: A prospective, single arm, multi-center study to assess the safety and performance of Neqstent in adjunctive therapy (CAFI Study)

CIP Document Number: DNQS428-01

CIP Revision: F

CIP Date: **15-Jan- 2020**

Signature/Date: _____

L. Carol Holt, MS, RN

Vice President, Clinical Affairs

Cerus Endovascular, Inc.

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18 APPENDIX C - Report of Prior Investigations

18.1 Human Use for Neqstent (Subject device)

All human use to date with Neqstent is compassionate use described in **Table** 10.

Table 10 Neqstent Compassionate Use

Country	Site	Treating MD	Date	Patient Initials	Procedure	Implants
Denmark	Odense University Hospital	Gyula Gal	21 Aug 2017	SP	Successful implant	7
			12 Oct 2017	PT	Successful implant	
			04 Dec 2017	DB	Successful implant	
			13 Mar 2018	KN	Successful implant	
			24 Oct 2018	LP	Successful implant	
			11 Dec 2018	BB	Successful implant	
			28 Feb 2019	BB	Successful implant	
Greece	Athens Euroclinic	Christos Gkogkas	01 Aug 2018	HK	Successful implant	2
			01 Aug 2018	ED	Successful implant	
Canada	Edmonton	Cian O'Kelly	14 Dec 2018	Not available	Successful implant	5
			13 Feb 2019	Not available	Successful implant	
			13 Feb 2019	Not available	Successful implant	
			07 Jun 2019	Not available	Successful implant	
			07 Jun 2019	Not available	Successful implant	
United States	Stony Brook University, New York	David Fiorella	11 Feb 2019	TL	Successful implant	1
Total Compassionate Use as of June 2019						15

18.2 Human Use for Contour (First generation device)

Study/ Assessment	Location	System	Current Status	Clinical Data Type	Number of Patients
Compassionate Use	AR (First in Human)	CNS	Completed	Compassionate Use	4
	UK				3
	DK				4

Study/ Assessment	Location	System	Current Status	Clinical Data Type	Number of Patients
INCA study	Clinica Familia Sagrada, Buenos Aires	CNS	Enrollment Closed	Feasibility	3
Pilot Study	United Kingdom Hungary	CNS	Enrollment Closed	Safety and Performance	19
CERUS Study	Germany, Denmark	CNS	Enrolling	Pre-Market	29 (as of June 2019)
TOTAL					**62**

18.3 Pre-Clinical Evaluation and Testing

18.3.1 Table 11 lists pre-clinical evaluation/testing criteria and results for systems that incorporates all Implant sizes.

Table 11 Pre-Clinical Evaluation Criteria and Results

Evaluation Criteria	*Results*
Biocompatibility • Biological Risk Assessment	Pass
Sterility • Sterility Assurance Level 10^{-6}	Pass
Ethylene Oxide Sterilant Residuals • Below limits in applicable standard	Pass
Nonpyrogenicity (Bacterial Endotoxin Testing) • 2.15 Endotoxin Units/device maximum	Pass
Implant Magnetic Resonance Imaging (MRI) Compatibility • MR Conditional to 3 Tesla per applicable standards	Pass
Implant Dimensions and Size Selection • Conformance with dimensional specifications • Implant wire integrity after 3 cycles through Introducer • IFU contains Implant size selection recommendations	Pass

Evaluation Criteria	*Results*
Implant Preparation and Placement Into Microcatheter • Conformance with dimensional specifications • Simulated use testing • Animal studies	Pass
Implant Radiopacity • Materials meet specifications • Conformance with dimensional specifications • Animal studies	Pass
Implant/DPW Deliverability and Deployment • Conformance with dimensional specifications • Implant/DPW deployment force testing • Animal studies	Pass
Implant Retraction • Implant/DPW retraction force testing • Implant wire integrity after retraction force testing • Implant/DPW tensile strength testing • Animal studies	Pass
Implant Detachment Reliability • Conformance with dimensional specifications • Implant detachment time testing • Animal studies	Pass
Implant Safety and Function After Implantation • Conformance with dimensional specifications • Animal studies	Pass

18.3.2 Animal Study Results

The Neqstent implant has undergone 2 animal studies as summarized in Table 8. The first study was a feasibility study while the second study was a GLP study. These studies were done to validate the design and performance of the implant during use similar to that occurring in humans. The animal models used in the testing process have been either elastase model or surgical creation of aneurysm. The rationale for using both models has been to establish performance characteristics in a range of aneurysm diameters and morphologies.

An induced experimental model is required to investigate novel treatments for IAs as these occur spontaneously only very rarely in animals. The rabbit model[2] has evolved over recent years as the species of choice for endovascular ICA due to three main factors:

1. The coagulation system of the rabbit is similar to that of humans.
2. The dimensions of the extracranial carotid arteries are similar to those of the intra-arterial cerebral artery dimensions in humans.
3. Rabbits are easier to handle and manage.

Surgically created aneurysms were used in this study in order to create large enough aneurysm to accommodate the Neqstent device in wide neck aneurysms and provide a large enough aneurysm sac to permit the passage of a microcatheter to deliver embolic coils. Technical development of the model has evolved so that an experimental aneurysm model similar to those observed in humans with regard to arterial origin, shape, hemodynamics and patency can be reproduced.

Measurement of performance characteristics has been undertaken at each study to inform the design development and evolve the design input.

Throughout animal testing, the product deliverability was excellent without presenting any unforeseen issues. The results are summarized in Table 12.

Table 12 Summary of Animal Studies

Study	Location	Number of Animals (one aneurysm per animal)	Survival	Findings
1	Research Institute of Neurointervention Paracelsus Medical University Christian Doppler Medical Center Salzburg Austria	*6	Chronic 30 days	Device placement easily achieved in 6/6 aneurysm. Implants were delivered by 2 physician operators. Parent vessels remained patent in 6/6 Immediate reduction in flow was seen in 5/6 Intra-aneurysmal thrombus seen in 4/4 Histopathology in 30-day specimen showed thrombosis in aneurysm with the establishment of a fine layer of neointima and all devices remained in position with no movement or migration observed.
2	Institute of Neurointervention Paracelsus Medical University Christian Doppler Medical Center Salzburg Austria)	14 rabbits (surgically created aneurysms)* 12 study rabbits 2 back-up rabbits	Chronic 6 – 30 days 6 – 60 days	Device placement easily achieved in 12/12 aneurysm. Implants were delivered by 2 physician operators. All Neqstent devices remained stable during the coiling procedure. Not all aneurysms were densely packed to assess their closure in follow-up Parent vessel remained patent in all subjects at the 30 day and 60 day time points. At 30 days Raymond Roy <II observed in 80% of the subjects. 60 days showed similar results. All devices remained stable at the neck in follow-up with no device herniation into the parent vessel

18.4 Conclusion

The Neqstent device has been subjected to appropriate testing to ensure appropriate safety and efficacy for clinical assessment as recommended in MEDDEV guidelines.

Preclinical use of the implant has demonstrated the ability to safely deploy and retract the implant into an appropriate position in the neck of the aneurysm using standard endovascular techniques under fluoroscopic guidance as per current standard of care.

Histopathological results in the preclinical phase have demonstrated the development of organized thrombus in the aneurysm sac and the development of endothelial tissue across the neck of the aneurysm encapsulating the implant and coil mass into the aneurysm wall.

The implant has undergone a range of biological and mechanical assessments as described above together with a thorough risk analysis to determine readiness for clinical evaluation.

19 APPENDIX E – Data Management Plan

DNQS428-06.B

(9 Pages)

20 APPENDIX F – Case Report Form CRF

DNQS425-F1.B EU EDC Study Worksheets – NQS

(38 Pages)