CorPath® GRX Neuro Study Protocol

An Evaluation of Effectiveness and Safety of the CorPath® GRX System in Endovascular Embolization Procedures of Cerebral Aneurysms

Clinical Protocol Number: 104-08660

Sponsored by:

Corindus, Inc.
309 Waverley Oaks Road, Suite 105,
Waltham, MA 02452
USA

Rev. I

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PROTOCOL SIGNATURE PAGE FOR PRINCIPAL INVESTIGATOR

I agree to perform and conduct the clinical investigation as described in the protocol and in accordance with the relevant parts of the International Conference on Harmonization (ICH) Guidelines for GCP, ISO 14155:2020(E), the Medical Device Regulation (2017/745) of 5 April, 2017, the Declaration of Helsinki, and the pertinent individual country laws/regulations. In addition, I agree to provide all the information requested in the case report forms presented to me by the Sponsor in a manner to ensure completeness, legibility, and accuracy. I agree to actively enroll subjects into this clinical investigation.

I also agree that all information provided to me by the Sponsor, including pre-clinical data, protocols, case report forms, and any verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the clinical investigation. It is recognized that this information may be relayed in confidence to the Institutional Review Board/Ethics Committee and the Competent Authority.

In addition, no reports or information about the clinical investigation or its progress will be provided to anyone not involved in the clinical investigation other than the Sponsor, the Institutional Review Board/Ethics Committee, and the Competent Authority. Any such submission will indicate that the material is confidential.

_____

Site Principal Investigator Name (print)

_____ _____

Site Principal Investigator Signature Date

CORPATH GRX NEURO STUDY SUMMARY

TITLE	An Evaluation of Effectiveness and Safety of the CorPath® GRX System in Endovascular Embolization Procedures of Cerebral Aneurysms
SHORT TITLE	CorPath GRX Neuro Study
DEVICE	CorPath GRX System: • Bedside Unit consists of the Extended Reach Arm, Robotic Drive and single-use Cassette. • Interventional cock pit • Control console
REGULATORY STATUS	The CorPath GRX System is CE Marked effective March 27, 2019 (CE 549879).
INDICATION FOR USE	The CorPath GRX System is intended for use in the remote delivery and manipulation of devices during percutaneous coronary and vascular procedures, including the following commercial devices: • Guidewires • Rapid Exchange Catheters • Guide Catheters • Microcatheters • Embolization Coils • Coil Assist Stents
STUDY OBJECTIVE	The primary objective of this study is to evaluate the effectiveness and safety of robotic-assisted endovascular embolization procedures compared to objective performance criteria for traditional, manual operation based on the scientific literature.
STUDY DESIGN	This is a prospective, single-arm, international, multi- center, non-inferiority study to evaluate the effectiveness and safety of the CorPath GRX System for endovascular cerebral aneurysm embolization compared to historical controls. Subject selection requires a clinical indication for endovascular coil and/or stent-assist coiling embolization of cerebral aneurysms.
STUDY COORDINATING PRINCIPAL INVESTIGATOR	Dr. Michel Piotin Service de Neuroradiologie Interventionnelle Hôpital de la Fondation Rothschild 25-29 rue Manin F - 75940 Paris, France

SAMPLE SIZE

Up to 120 subjects will be enrolled in order to achieve at least 108 subjects in the study; each site will try to recruit a maximum of 20 subjects. If a site has the possibility to enroll more than 20 subjects, a written authorization will be required from the sponsor, Corindus, Inc.

INVESTIGATIONAL SITES

A maximum of up to 20 international sites may participate in this study. This will depend on each active site's recruitment rate and the possible travel restrictions due to the Covid-19 pandemic.

STUDY DURATION/ FOLLOW-UP PERIOD

The recruitment phase is 18 months, follow-up is 180-days, and total study duration is 24 months. All subjects will be followed post-CorPath GRX endovascular embolization procedure through 180-days.

SUBJECT POPULATION:

Subjects with a clinical indication for endovascular coil and/or stent-assisted coiling embolization of cerebral aneurysms.

INCLUSION CRITERIA

Candidates will be included in the study only if all the following conditions are met:

1. Age ≥ 18 years.
2. At least one cerebral aneurysm (unruptured) with indication for endovascular treatment; dome to neck ratio >1.5 or aneurysm neck width >4.0 mm.
3. The Investigator deems the procedure appropriate for both manual or robotic-assisted endovascular treatment.
4. The conscious subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent.

EXCLUSION CRITERIA

Candidates will be excluded from the study if any of the following conditions are present:

1. Failure / unwillingness of the subject to provide informed consent.
2. The Investigator determines that the subject or the neurovascular anatomy is not suitable for robotic-assisted endovascular treatment.
3. Women who are pregnant.
4. Persons under guardianship or curatorship.

ELIGIBILITY COMMITTEE

The Eligibility Committee will be responsible for the evaluation of CorPath GRX Neuro subjects for participation in the study. In advance of all study subject enrollment and treatment, the committee will use subject clinical history, Unruptured Intracranial Aneurysm Treatment Score (UIATS) data, the treatment plan, and at least 4 angiographic (DSA or CTA/MRA) images to approve for inclusion into the study or exclude and defer treatment of the cerebral aneurysm with the CorPath GRX Robotic system.

PRIMARY EFFECTIVE-NESS ENDPOINT

The primary effectiveness endpoint will be defined as successful completion of the robotic-assisted endovascular procedure absent any unplanned conversion to manual for guidewire or microcatheter navigation, embolization coil(s) or intracranial stent(s) deployment, or an inability to navigate vessel anatomy.

PRIMARY SAFETY END- POINT

The primary safety endpoint will be a composite of intra- and peri-procedural events, defined as vascular injury including intra-procedural aneurysm rupture caused by robotically controlled catheters, wires, or devices and thromboembolic events with neurological decline (NIHSS score change ≥ 4) within 24-hours post- procedure or hospital discharge, whichever occurs first.

SECONDARY END-POINTS

Clinical Outcome
Clinical outcome as measured by Modified Rankin Scale. This is assessed at the 90-Day Follow-Up (± 14 days) and at the 180-Day Follow-Up (± 30 days from the procedure date);

Robotically Navigate Device *to* the Target Aneurysm
Defined as successful advancement of device to the target aneurysm robotically;

Robotically Navigate Device *into* the Target Aneurysm
Defined as successful navigation of device into the target aneurysm robotically;

Robotically Deploy Therapeutic Device *into* the Target Aneurysm Defined as successful deployment of therapeutic device into the tar- get aneurysm robotically;

Overall Procedure Time
Defined as the time measured from the insertion of the access sheath/catheter until the removal of the microcatheter;

Robotic Procedure Time
Defined as the time measured from the first device used robotically until the removal of the microcatheter;

Fluoroscopy Time
Total fluoroscopy utilized during the procedure as recorded by the Imaging System;

Patient Radiation Exposure
DAP (dose-area-product) and CD/AK (cumulative dose/air kerma) as recorded during the procedure;

Contrast Volume
Total contrast used during the procedure;

Adverse Events
All adverse events (AEs) from the start of the CorPath GRX procedure until the end of the study will be summarized;

Thromboembolic Events
Defined as rate of thromboembolic events occurring up to 180-days following the robotic-assisted procedure.

Devices Used Robotically
All devices used will be recorded as successful or unsuccessful in conjunction with the CorPath GRX System;

Aneurysm Occlusion
Angiographic assessment of aneurysm occlusion grade according to the Raymond-Roy classification scale, parent-vessel compromise, and occlusion durability as assessed from an independent core laboratory. This will be assessed post-procedure and at a 180-day follow-up.

STUDY SPONSOR

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MANUFACTURER

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MONITORING SERVICE	Corindus, Inc. 309 Waverley Oaks Road, Suite 105 Waltham, MA 02452 USA Alan Cohen (Europe) Cohen's Clinical Consultants Paul Parmentierlaan 180/01 B – 8300 Knokke, Belgium Tracey Edinburg (Australia Manager Director) ReSQ Clinical Research 2/40 Hardy St. Dover Heights, NSW, Australia 2030
DATA COORDINATING & MONITORING CENTER	MedNet Solutions, Inc. 110 Cheshire Lane, Suite 300 Minnetonka, MN 55305 USA
ANGIOGRAPHIC CORE LABORATORY	David S Liebeskind, MD Neurovascular Imaging Research Core UCLA Department of Neurology Las Angeles, CA 90095 USA
STATISTICAL ANALYSIS SERVICES	Technomics Research 1815 Medina Rd. Long Lake, MN 55356 USA

SCHEDULE OF ACTIVITIES

	Pre-Procedure	Procedure	Post-Procedure	90-day[7] ***BY PHONE***	180-day	Un-Scheduled Visit
		Day (0)	(24-hours post-procedure or hospital discharge)	±14-days	±30-days	
Patient Eligibility Criteria	X					
Submit to Eligibility Committee • Clinical history • Unruptured Intracranial Aneurysm Treatment Score • Treatment plan • ≥ 4 angiographic (DSA or CTA/MRA) images	X					
Medical History	X[1]					
Digital Subtraction Angiography (DSA), Computed Tomography Angiography (CTA), or Magnetic Resonance Angiography (MRA)/Magnetic Resonance Imaging (MRI) of the brain/head	X[1]				X[7]	
Clinical assessment & Physical exam including: • Modified Rankin Scale (mRS) • National Institutes of Health Stroke Scale (NIHSS) scale	X		X	X[6]	X[8]	X[9]
Raymond Grade-Roy Occlusion Classification Scale	X[3]	X			X	
Laboratory Tests: hemoglobin, hematocrit, activated partial thromboplastin time, platelet count, international normalized ratio, pregnancy test, serum creatinine and glomerular filtration rate.	X[1,2,4]		X[2]			
Procedure Parameters		X				
Catheter Angiography		X[5]				
Contrast volume		X				
Record of AEs		X	X	X	X	X
Data for aneurysm assessment e.g. tortuosity, proximal & distal vessel diameter, target aneurysm measurements.		X			X	

[1] Within 7 days of index procedure.

[2] If performed under standard hospital procedure.

[3] For previously coiled aneurysms.

[4] Female subjects of child-bearing potential must have negative pregnancy test (urine or serum).

[5] Includes angiograms in the anterior posterior, lateral and working positions for analysis by a core laboratory.

[6] Telephone assessment and mRS is required. Other post procedure clinical assessment (scales/scores/grades) is left to the discretion of the investigator and shall be dictated by the patient's clinical symptoms.

[7] Post scans will be sent to the core laboratory for analysis.

[8] mRS is required. Other post procedure clinical assessment (scales/scores/grades) is left to the discretion of the investigator and shall be dictated by the patient's clinical symptoms.

[9] If visit is related to target aneurysm or potentially associated AE/SAE

1. INTRODUCTION

1.1 Device Name

CorPath® GRX System

1.2 Background

Subarachnoid hemorrhage is a life-threatening form of stroke with an estimated fatality rate between 26 and 36%.[1–3] In approximately 80% of cases, subarachnoid hemorrhage is caused by the rupture of an intracranial saccular aneurysm.[1] Aneurysms occur when structural abnormalities in the walls of the cerebral arteries cause weakening, thinning, and out-pouching of the vessel wall. They are frequently located at bifurcations within the proximal circle of Willis and approximately 20-50% of such aneurysms eventually rupture. While the incidence of subarachnoid hemorrhage varies widely from country to country and may be as high as 15 to 20 per 100,000 in Finland and Japan, its overall worldwide incidence is estimated to be 9.1 per 100,000 persons.[4] As many as 30,000 Americans are affected per year.[1–3,5–7]

Patients who survive subarachnoid hemorrhage long enough to be stabilized medically may experience cerebral vasospasm, delayed cerebral ischemia, hydrocephalus, deep venous thrombosis, and numerous medical sequelae, along with long-lasting neuropsychological changes, loss of productive years, and diminished quality of life.[1–3,6–8] They are also at serious risk of re-rupture, and therefore it is usually appropriate for them to undergo treatment to minimize aneurysmal recurrence or re-rupture.

Meanwhile, it has been estimated that the remaining 50% to 80% of intracranial aneurysms present in the general population never rupture.[9,10] The prevalence of unruptured intracranial aneurysms (UIA) in the general adult population has been estimated at between 1% and 5%, based on autopsy studies.[10] Many are asymptomatic and detected only as incidental findings during cerebral imaging for other conditions. Others may cause headaches, seizures, cranial nerve palsies, focal neurologic deficits, and distal embolic ischemic events.[11]

Due to the severe consequences of aneurysmal rupture, once a UIA is detected, a decision must be made between managing the patient conservatively or treating the aneurysm to prevent future rupture. While current clinical evidence favors treatment for ruptured aneurysms,[3,7] the

decision to intervene for UIA is less straightforward [12,13] and must balance the risk-benefit profile of the available interventions against the risks and benefits of watchful waiting.[9,10,14–17]

Whether to prevent primary rupture of a UIA or re-rupture following a subarachnoid hemorrhage event, the principal treatment options are open surgical clipping or endovascular coiling.[3,7,8,10,13] Surgical clipping involves a craniotomy, through which the aneurysmal sac is closed mechanically by placing a titanium clip over the neck. Endovascular coiling is achieved percutaneously by threading a catheter from the femoral artery, accessed at a site in the groin, up through the arterial circulation to the neck of the aneurysm. Using the catheter as a guide, a smaller microcatheter is then advanced through the guide catheter to the target aneurysm. After placement of the microcatheter, a metal wire is inserted into the microcatheter and advanced up to and into the aneurysmal sac, where the wire is gently pushed forward, causing it to coil around itself until it fills the volume of the sac. The presence of the metal coil induces thrombosis, occluding the aneurysm and preventing turbulent or high-pressure blood flow that is the precursor to thrombogenesis or rupture.

Available evidence is not sufficient to definitively favor one technique over the other, but some randomized clinical trials have suggested that surgical clipping is effective and durable, while minimally invasive endovascular approaches result in better functional outcomes after 1 year.[18,19] Presumably this difference is a result of the higher overall risks of open surgery com- pared to minimally invasive procedures. Nonetheless, the pace of adoption of percutaneous aneurysm coiling and other neuro-endovascular techniques continues to accelerate, and therefore there is advantage to the continuous development of technical measures that can improve their safety.

The risks of endovascular approaches generally fall into categories similar to those observed in percutaneous coronary and peripheral vascular intervention (PCI and PVI) and include intraprocedural rupture, arterial dissection, pseudoaneurysm, thromboembolism, occlusion of parent arteries, and groin hematomas and infections.[10,14–16,20–25] Patients can also experience adverse reactions to the contrast material necessary for visualization of the procedure under fluoroscopy.

As a radiation-dependent imaging technique, fluoroscopic navigation further poses occupational risks to the clinical staff performing the procedure. Data from studies on healthcare professionals working in cardiac catheterization labs have suggested that long-term exposure to low-dose ionizing radiation is linked to elevated risk of cataracts, skin lesions, thyroid disease, premature vascular aging, and cancer compared to healthcare professionals not routinely exposed to occupational fluoroscopy.[26–28] Furthermore, the protective clothing worn to shield interventionalists from fluoroscopy is bulky, heavy, and puts the clinical staff at non-trivial risk of ergonomic strain and orthopedic injury.[26]

The advent of the CorPath GRX Robotic System for PCI and later for PVI has begun to address some of the limitations of endovascular intervention.[29–37]

The CorPath GRX system translates the manual movements of the interventionalist into precision micromovements during navigation and facilitates precision measurement of anatomy to determine lesion length.[38,39] It also allows the procedure to be performed from a remote, radiation-shielded workstation, which may help to reduce the interventionalist's exposure to ionizing radiation and orthopedic strain.[34]

The field of neurosurgery also stands to benefit from the use of robotic assistance.[40] To date, the ROSA robot (Zimmer Biomet, Warsaw IN, USA) has been FDA cleared and CE marked for epilepsy evaluation and spine surgery,[41] the Modus V robotically operated exoscope (Synaptive Medical, Toronto, ON, Canada) is FDA cleared for subcortical surgery,[42] and the Renaissance Surgical Guidance Robot (Mazor Robotics, Caesarea, Israel) is FDA cleared and CE marked for spine surgery.[43]

However, until recently, no robotic platform has been designed to accommodate the micro guidewires, microcatheters, and micro-scale movements specific to successful neurovascular intervention.

Based the findings of an initial evaluation of the system in *in vitro* and animal neurovascular models,[44] Corindus has recently implemented software and engineering modifications to its Cor-Path GRX Robotic System to address neuro-endovascular-specific needs and indications.

These modifications include:

1) A software feature called “Active Device Fixation (ADF)”. When enabled, ADF maintains the placement of both the guidewire and device while the catheter is advanced or retracted by advancing or retracting the guidewire and device to off-set the motion of the catheter.
2) A software feature called “Limited Speed”. When enabled, Limited Speed reduces the linear movement of the guidewire or device by half, capping its maximum speed at a rate of 6 mm/sec.
3) Physical modifications to the hardware to securely and reliably accommodate the smaller gauge devices common to percutaneous neurosurgery.
4) Software modifications to allow for increased working length to enable target access for microcatheters and an updated user interface to accommodate the new workflow and automated movements. These new features have been further evaluated in vitro and in vivo, with results that suggested that clinical development of the modified system is war- ranted (Britz et. al., 2019, Manuscript in Preparation).

The present clinical study is a prospective, single-arm, international, multi-center, non-inferiority study to evaluate the effectiveness and safety of the CorPath GRX System for endovascular cerebral aneurysm embolization compared to historical controls through 24-hours post-procedure or hospital discharge, whichever occurs first.

2. INTENDED USE & DEVICE DESCRIPTION

2.1 Intended Use

The CorPath GRX System is intended for use in the remote delivery and manipulation of interventional devices during percutaneous coronary and vascular procedures, including the following commercial devices:

- Guidewires
- Rapid Exchange Catheters
- Guide Catheters
- Microcatheters
- Embolization Coils

- Coil Assist Stents

2.2 Device Description and Mode of Operation

The CorPath GRX System is designed to allow the operator to remotely manipulate interventional devices within a patient's vasculature to perform vascular procedures in a precise and well-controlled fashion, without being exposed to radiation levels typically encountered during a conventional (i.e. manual) procedure. The complete CorPath GRX System includes the following major components:

2.2.1 Bedside Unit

The Bedside Unit consists of an Extended Reach Arm, Robotic Drive, and Single-use Cassette.

- Extended Reach Arm: Mounted on the rail of the procedure table and supports the Robotic Drive.
- Robotic Drive: Receives inputs from the Control Console. These inputs actuate mechanical operations in the Single-use Cassette as movements to a loaded guidewire, device, and guide catheter/microcatheter. The Robotic Drive moves forward and backward to advance and retract the guide catheter or microcatheter. A Bedside Touchscreen on the Robotic Drive provides the user interface for the bedside operator during system set-up, loading, and device exchanges.
- Single-use Sterile Cassette: Attaches to the Robotic Drive and can be loaded with commercially available guidewires, rapid exchange catheters, guide catheters, microcatheters, neuro- vascular stent retrievers, embolization coils, and intracranial stents. This Single-use Cassette advances and retracts the guidewire, device and catheter, with the ability to rotate the guidewire and catheter.

***Note**: Refer to specific interventional device instructions for proper device use.*

2.2.2 Interventional Cockpit

The interventional cockpit houses the Control Console, X-ray Foot Pedal, and Monitor(s) to dis- play angiographic and hemodynamic data. It is designed to protect the physician from radiation exposure while maneuvering interventional devices.

2.2.3 Control Console

This component has a touchscreen and three joysticks (one joystick for device manipulation, one joystick for guidewire manipulation and one joystick for catheter manipulation). The device joystick allows for precise control of linear motion (advancement and retrieval) of its respective devices. The guidewire joystick allows for both linear and rotational movement (clockwise and counterclockwise) of the guidewire. The catheter joystick allows for precise control of linear motion (advancement and retrieval) and for rotational movement (clockwise and counterclockwise) of the guide catheter or microcatheter. The devices are controlled independently, which allows operations to be performed individually (by using one joystick at a time) or simultaneously (by activating multiple joysticks at once). For precise, discrete manipulation, the device, guidewire and catheter can also be manipulated in discreet 1-mm increments via the touch-screen buttons on the Control Console.

CorPath GRX features techniQ Smart Procedural Automation, a set of automated movements unique to the system. These movements include: Rotate on Retract (RoR), Limited Speed, and Active Device Fixation (ADF). Users may enable a techniQ by pressing on the dropdown menu on the corresponding section of the touchscreen on the Control Console.

Note: *For a more detailed description of the CorPath GRX System please refer to the CorPath GRX System Operator's Manual.*

2.2.4 Device Accountability

According to the ISO 14155:2020, Section I.7, part C, point 1, if a device is a market approved medical device being used within its approved indication, device accountability is not required. In addition, point 2 states that labelling specific for clinical investigations is also not required.

3. OBJECTIVES & ENDPOINTS

3.1 Study Objective

The primary objective of this study is to evaluate the effectiveness and safety of robotic-assisted endovascular embolization procedures compared to objective performance criteria based on the scientific literature.

3.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint will be defined as successful completion of the robotic-assisted endovascular procedure absent any unplanned conversion to manual for guidewire or microcatheter navigation, embolization coil(s) or intracranial stent(s) deployment, or an inability to navigate vessel anatomy.

3.3 Primary Safety Endpoint

The primary safety endpoint will be a composite of intra- and peri-procedural events, defined as vascular injury including intraprocedural aneurysm rupture caused by robotically controlled catheters, wires, or devices and thromboembolic events with neurological decline (NIHSS score change ≥ 4) within 24-hours post-procedure or hospital discharge, whichever occurs first.

3.4 Secondary Endpoints

Several secondary endpoints will be examined in this trial, including the following:

1. **Clinical Outcome -** Clinical outcome as measured by Modified Rankin Scale. This is assessed at 90-Day Follow-Up (± 14 days) and 180-Day Follow-Up (± 30 days from the procedure date);
2. **Robotically Navigate Device *to* the Target Aneurysm** - Defined as successful advancement of devices to the target aneurysm robotically;
3. **Robotically Navigate Device *into* the Target Aneurysm** - Defined as successful navigation of device into the target aneurysm robotically;
4. **Robotically Deploy Therapeutic Device *into* Target Aneurysm** - Defined as successful deployment of therapeutic device into the target aneurysm robotically;
5. **Overall Procedure Time** - Defined as the time measured from the insertion of the access sheath/catheter until the removal of the microcatheter;

6. **Robotic Procedure Time** - Defined as the time measured from the first device used robotically until the removal of the microcatheter;
7. **Fluoroscopy Time** - Total fluoroscopy utilized during the procedure as recorded by the Imaging System;
8. **Patient Radiation Exposure** - DAP (dose-area-product) and CD/AK (cumulative dose/air kerma) as recorded during the procedure;
9. **Contrast Volume** - Total contrast used during the procedure;
10. **Adverse Events** - All adverse events (AEs) from the start of the CorPath GRX procedure until the end of the study will be summarized.
11. **Thromboembolic Events** - Defined as rate of thromboembolic events occurring up to 180-days following the robotic-assisted procedure;
12. **Devices Used Robotically** - All devices used will be recorded as successful or unsuccessful in conjunction with the CorPath GRX System;
13. **Aneurysm Occlusion** - Angiographic assessment of aneurysm occlusion grade according to the Raymond-Roy classification scale, parent-vessel compromise, and occlusion durability as assessed from an independent core laboratory. This will be assessed post-procedure and at a 180-day follow-up.

4. INVESTIGATIONAL PLAN

4.1 Overview of Trial Design

This is a prospective, single-arm, international, multi-center, non-inferiority study to gather real-world data on the effectiveness and safety of the CorPath GRX System for endovascular cerebral aneurysm embolization. Subject selection requires a clinical indication for endovascular coil and/or stent-assisted coiling embolization of cerebral aneurysms. After obtaining informed consent, performing eligibility confirmation, then screening and baseline assessments, qualifying subjects will be enrolled in the clinical investigation.

The study will be conducted at a maximum of up to 20 investigational sites. This will depend on each active site's recruitment rate and the possible travel restrictions due to the Covid-19 pandemic. Up to 120 subjects will be enrolled in order to achieve at least 108 subjects in the study; each site will try to recruit a maximum of 20 subjects. If a site has the possibility to enroll

more than 20 subjects, a written authorization will be required from the sponsor, Corindus, Inc. The protocol does not dictate the therapeutic decisions of the Investigators. The total expected maximum *clinical investigation duration*, including completion of all follow-up requirements, is approximately 24 months: the recruitment phase is 18 months and follow-up is 180-days. No further follow-up or additional treatment is required per the protocol, and any additional follow-up and/or treatment is at the discretion of the physician/standard hospital practices.

All enrolled subjects will be followed post-CorPath GRX endovascular procedure through 180 days post-procedure.

4.2 Roll-in Subjects

The primary purpose of the roll-in subjects is to allow the Investigator to gain experience with the CorPath GRX System in the setting of the clinical trial. This will also ensure familiarity with protocol requirements. The first three (3) subjects for each primary Investigator will be considered as roll-in subjects. Subjects entered in the roll-in phase will complete all follow-up requirements of 180-days.

4.3 Enrollment Plans

Each consecutive patient undergoing a CorPath GRX cerebral aneurysm endovascular procedure will be enrolled in the study after providing written informed consent for the provision of data.

4.4 Informed Consent Procedures

This protocol requires written informed consent, in accordance with applicable country and clinical investigation site regulations. This consent shall be obtained from each conscious subject prior to the investigational procedure. The subject will have at least 24 hours to consider if he/she wants to participate in the study (if required by EC).

Although not indicated in the Patient Information Sheet, in certain countries, the Ethics Committee requires that all subjects included in the clinical investigation be affiliated with their respective national social security system. It is up to the investigator to find out if the subject has this required affiliation.

Prior to starting the clinical investigation, Corindus will provide the Principal Investigator with a

copy of the Informed Consent Document approved by the Ethics Committee (EC) and the Competent Authority (if applicable), with documented evidence that the protocol has received EC and Competent Authority (if applicable) approvals.

A thorough written explanation will be provided to the subject as to the nature and objectives of this study. Details of the study should include (but are not limited to) the following terms:

- Purpose of the study
- Alternative treatments
- Participation is voluntary, and there is no penalty for withdrawal
- Potential risks/benefits for participation
- Contact information to ask questions or voice concerns

This discussion should highlight the fact that the patient is being asked solely to share the data collected from their endovascular robotic procedure and any related events through 24-hours post-procedure or discharge, whichever occurs first. The study investigator and/or staff are responsible for obtaining written informed consent from each potential subject before any study specific procedures required by the protocol are performed. Informed consent should be obtained in written format and using a form approved by the EC and Competent Authority. The form should contain standard language consistent with local policies for ensuring privacy of confidential information. All subjects must sign the informed consent prior to any procedures/tests that go beyond initial assessments associated with the standard care for subjects with cerebral aneurysms and before any study related treatment assessments are administered and subject-related health information can be entered into the study database.

Subjects are considered enrolled in the study once the subject signs the study Informed Consent Form. Failure to obtain signed informed consent, renders the subject ineligible. For those subjects that sign informed consent, a copy shall be kept in the subject's medical records and study files. A copy of the fully executed informed consent form must be given to each subject enrolled in the study.

4.5 Screen Failure

A subject who signs an informed consent form (ICF) and does not have a CorPath GRX endo-vascular procedure or is enrolled in the study but withdraws their consent will be considered a screen failure. However, all data collected from the enrolled subject prior to the time of consent

withdrawal will be included in the analysis.

4.6 Patient Selection

Subjects with a clinical indication for endovascular coil and/or stent-assist coiling embolization of unruptured cerebral aneurysms. Subjects who meet all inclusion criteria while exhibiting none of the exclusion criteria (see below) and have signed the informed consent will be considered enrolled. All eligible subjects will be evaluated using the Corindus CorPath® GRX System in Endovascular Embolization Procedures of Cerebral Aneurysms.

4.6.1 INCLUSION CRITERIA

1. Age ≥ 18 years.
2. At least one cerebral aneurysm (unruptured) with indication for endovascular treatment; dome to neck ratio >1.5 or aneurysm neck width >4.0 mm.
3. The Investigator deems the procedure appropriate for both manual or robotic-assisted endovascular treatment.
4. The conscious subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent.

4.6.2 EXCLUSION CRITERIA

1. Failure / unwillingness of the subject to provide informed consent, unless the EC has waived informed consent.
2. The Investigator determines that the subject or the neurovascular anatomy is not suitable for robotic-assisted endovascular treatment.
3. Women who are pregnant.
4. Persons under guardianship or curatorship.

4.6.3 Eligibility Committee

The Eligibility Committee will be responsible for the evaluation of CorPath GRX Neuro subjects for participation in the study. In advance of all study subject enrollment and treatment, the committee will use subject clinical history, Unruptured Intracranial Aneurysm Treatment Score (UIATS) data, the treatment plan, and at least 4 angiographic (DSA or CTA/MRA) images to approve for inclusion into the study or exclude and defer treatment of the cerebral aneurysm with the CorPath GRX

Robotic system.

The Eligibility Committee will be comprised of three neurovascular subject matter experts with experience in the treatment of cerebral aneurysm, data and imaging interpretation, and clinical research trials. They must be neurointerventionalists qualified by training, experience with the CorPath GRX robotic system, and CorPath GRX Neuro Study training.

Once investigative sites are qualified to recruit study subjects, subject imaging, UIATS data, treatment plan, and clinical history will be uploaded to the Oculus Imaging Portal for the committee to review. Neuroimaging will be obtained within 3 months of the eligibility evaluation and will include at least 4 cerebrovascular images with measurements of the targeted cerebral aneurysm, as well as imaging of the parent vessel and aortic arch. Clinical evaluation of patients will include confirmation of all inclusion and no exclusion criteria being met, completion of an UIATS form with applicable treatment justification as needed, and any other applicable medical history required to allow the Eligibility Committee assessment. Additionally, planned procedural devices including Guidewire, Microcatheter, Stent, and Coils will be included.

Upon completion of training on the use of the Oculus Imaging Portal, the Eligibility Committee members will assess the submitted subject data and make a determination on whether a subject qualifies for treatment in the CorPath GRX Neuro Study.

4.7 Subject Withdrawal and Replacement

Subjects enrolled in the study can discontinue their participation at any time for any reason without prejudice or reduction in the quality of their medical care. The investigator can terminate a subject's participation in the study to protect the subject's health, if the subject fails to follow instructions or if the subject is unable to keep appointments. The Investigator must then document this notification of withdrawal from the study in the appropriate CRF and notify the sponsor. No replacements will be allowed. Up to 120 subjects will be enrolled in order to achieve data on 108 subjects. All data will be included in summaries.

4.8 Data to Be Collected

4.8.1 Peri-procedural Study Medication Regime

Sites are to follow standard institutional and/or coil/stent manufacturer's guidelines for recommended anticoagulation regimen.

4.8.2 Baseline Date

The following baseline data ***should*** be collected for all subjects prior to the planned index procedure (usually routinely done for endovascular robotic procedure subjects with cerebral aneurysms):

- Patient Eligibility Criteria
- Head CT angiography or MR angiography
- Demographics
- Medical history
- Pre-endovascular Patient Assessment conducted by a trained person with appropriate qualifications to perform these evaluations:
    - Modified Rankin score
    - Raymond Grade for previously coiled aneurysms
    - National Institutes of Health Stroke Scale (NIHSS) scale
- Laboratory tests, if performed under standard hospital procedure, *should* be collected for all subjects prior to planned index-procedure (usually routinely done for patients undergoing cerebral aneurysm endovascular procedure *):
    - Hemoglobin (HGB)
    - Hematocrit (HCT)
    - Activated Partial Thromboplastin Time (aPTT)
    - Platelet count
    - International Normalized Ratio (INR)
    - Pregnancy test
    - Serum creatinine
    - Glomerular Filtration Rate (GFR)

**** Note**: Pre-endovascular Patient Assessment and laboratory tests must be within 7 days of index procedure. Female patients of child-bearing potential must have a negative pregnancy test (serum or urine).*

4.8.3 Data Collection Prior To Initiating CorPath Procedure

- Arterial access site
- What devices will be planned for robotic delivery
- Procedure Start Time (Sheath insertion)

4.8.4 Data Collection During CorPath Procedure

- Fluoroscopy time
- Patient radiation exposure (dose-area-product [DAP] and air kerma [AK])
- Aneurysm Assessment
- Contrast volume
- Endovascular procedure End Time (microcatheter out-time)
- Record of all Adverse Events (AE)

***Note**: A de-identified copy of all the procedural angiograms will be sent directly to the imaging core lab.*

4.8.5 CorPath GRX Endovascular Procedure Workflow

The protocol allows for the Investigator to perform the following with the CorPath GRX System:

- Navigate a 0.014" guidewire in the neurovascular anatomy;
- Navigate a microcatheter into the neurovascular anatomy robotically;
- Navigate a microcatheter to the aneurysm robotically;
- Navigate treatment devices (coils/stents) to the aneurysm robotically;
- Deploy treatment devices into the aneurysm robotically.

The Investigator should refer to the CorPath GRX System Operator's Manual for a detailed description of the system and relevant techniques.

After arterial access is obtained, the Investigator will specify what devices will used robotically prior to starting the robotic portion of the endovascular procedure.

CorPath Use Technique

To obtain proper data for analysis, the following procedure, with associated data collection mile-stones, is recommended, but in no case, dictates use of the CorPath GRX System in a manner

different from that presented in the Operator's Manual.

The following CorPath Use Technique guides the Investigator through coiling a cerebral aneurysm with the CorPath GRX System.

1. Obtain arterial access using conventional technique. Record sheath insertion time.
2. Once arterial access is obtained, insert a standard diagnostic catheter using conventional manual technique or guide catheter mounted coaxially over a diagnostic insert catheter.
3. Manually advance the diagnostic select catheter to the parent vessel.
4. Advance guide catheter to desired location in parent vessel and remove wire and diagnostic select catheter. If only diagnostic catheter was used, then remove standard wire and use exchange length guidewire; remove the diagnostic catheter over the exchange wire while maintaining distal wire position. Advance the guide catheter over the exchange wire to the desired location in parent vessel and remove wire.
5. The Investigator will specify which devices will be delivered robotically.
6. Manually advance microcatheter to tip of guide catheter in the parent vessel.
7. Manually insert exchange length guidewire and attach COPILOT bleed back control valve to the microcatheter.
8. Record microcatheter "insertion" time.
9. Load the microcatheter and exchange length guidewire in the CorPath GRX cassette.
10. Using the CorPath System, advance guidewire and microcatheter independently to tar- get treatment area. The Active Device Fixation (ADF) technIQ automated movement can be enabled to keep the guidewire in place during microcatheter movement.
11. With microcatheter in place, remove guidewire.
12. Advance stent into the COPILOT bleed back control valve and proximal microcatheter slowly and according to stent delivery IFU.
13. Place the stent advancement wire into the Device Track of the CorPath GRX.
14. Advance stent, robotically, to target area. The stent will remain completely sheathed in the microcatheter.
15. Robotically position the stent across target aneurysm.
16. Maintaining stent position with CorPath GRX, begin to robotically remove the microcatheter with ADF enabled on the microcatheter. This will unsheathe the stent in place.
17. Using micro-millimeter movements with the CorPath GRX, continue to remove micro- catheter until stent is completely unsheathed and fully deployed.
18. Remove stent deployment shaft robotically, reload exchange length guidewire, and re- advance guidewire to target aneurysm.
19. Using robotic manipulation, advance the microcatheter and guidewire wire to position through the stent struts.
20. Robotically retract guidewire.
21. Remove guidewire from cassette and load embolization coils into Device Track.
22. Using the CorPath System, advance embolization coils to target aneurysm. Slowly de-ploy embolization coils as per physician preference. The Limited Speed technIQ auto- mated movement may be enabled to slow maximum speed to 6mm/sec if

desired. De- tach and exchange embolization coils as per IFU.
23. After embolization of target aneurysm, robotically remove coil delivery catheter and microcatheter.
24. Perform final control angiography.
25. Record final fluoroscopy time, DAP, AK and contrast volume.
26. Record time of microcatheter “removal” time from the parent vessel.
27. Record Operator pocket dosimeter reading.

4.8.6 Specify Device to Be Used Robotically

After arterial access prior to using the CorPath GRX System, the Investigator will specify which device he/she will plan to use robotically. If a device that is used robotically cannot be delivered to the target, cross the target or delivered into the target and conversion to manual is needed, it will be documented as an unplanned conversion to manual.

4.8.7 Conversion to Manual Procedure Data Collection

The Investigator shall determine if it is necessary to convert to standard manual techniques to complete the endovascular robotic procedure. The Investigator should make this decision based on his/her medical assessment of the situation in accordance with the best interest of the subject. It is recommended that conversion to manual operation be performed at the discretion of the Investigator or if any of the following occur:

- The inability to navigate the guidewire(s), microcatheter(s), embolization coil(s) or stent-assist coiling using the CorPath GRX System as intended.
- Any clinical condition that requires rapid medical intervention. Details of manual technique to be documented are:
    - Planned or unplanned (e.g. physician preference, use of equipment not compatible with CorPath GRX);
    - If unplanned (e.g. embolization coils were undeliverable due to severe tortuosity), specify why.

4.8.8 Device Malfunction Data Collection

All CorPath GRX System device malfunctions will be documented in the EDC. If the device malfunction is related to a Device-Related Adverse Event (AE), the AE will be entered into the EDC and each site will follow their internal policies for AE reporting.

4.8.9 Post-CorPath Data Collection

Post-CorPath Procedure Medication Regimen

Follow standard operator and institutional routines for recommended anticoagulation and anti-platelet regimens.

Post-CorPath Procedure Subject Evaluations

- NIH Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) conducted by a trained person with appropriate qualifications to perform these evaluations are required to be performed within 24-hours post procedure or prior to discharge, whichever occurs first.
- Raymond Grade-Roy Occlusion Classification Scale conducted by a trained person with appropriate qualifications to perform this evaluation:
    - Class (I): Complete occlusion – complete obliteration of the aneurysm
    - Class (II): Residual neck – persistence of any portion of the original defect of the arterial wall as seen on any single projection, but without opacification of the aneurysmal sac.
    - Class (III): Residual aneurysm – opacification of the aneurysmal sac.
        - Class IIIa: contrast opacification within the coil mesh
        - Class IIIb: contrast opacification outside coil mesh
- Additional post procedure clinical assessment (scales/scores) is left to the discretion of the investigator and shall be dictated by the patient's clinical symptoms
- Record of all Adverse Events (AEs)
- If clinically indicated by the Investigator and/or if performed under standard hospital procedure, record lab values closet to 24-hours post-procedure or discharge:
    - Hemoglobin (HGB)
    - Hematocrit (HCT)
    - Activated Partial Thromboplastin Time (aPTT)
    - Platelet count
    - International Normalized Ratio (INR)
    - Serum Creatinine
    - Glomerular Filtration Rate (GFR)

- Before the subject is discharged from the hospital, it is recommended that telephone numbers and contact information be confirmed with the subject (and/or authorized legal guardian) to ensure the ability to contact him/her after discharge from the hospital for scheduling of the 90-day (± 14 days) telephone evaluation.

4.8.10 Follow-Up Evaluations

The following assessments will be completed at the specified time points below.

- **90-Day Follow-Up (± 14 days) via a telephone evaluation**
  - Functional outcomes assessment to include Modified Rankin Scale (mRS)
  - Record any adverse events or additional interventions since time of hospital discharge

Note: *If during the time of telephone contact, the subject reports any adverse events or additional interventions, the subject shall undergo an office visit, whereupon a neurological examination and any other additional testing deemed appropriate by the investigator shall be performed.*

- **180-Day Follow-Up (± 30 days)**
  - Digital Subtraction Angiography (DSA), Computed Tomography Angiography (CTA), or Magnetic Resonance Angiography (MRA) / Magnetic Resonance Imaging (MRI) of the brain/head
  - Functional outcomes assessment to include Modified Rankin Scale (mRS)
  - Raymond-Roy Occlusion Classification
  - Record any adverse events or additional interventions since time of hospital discharge.

4.8.11 Schedule of Data Collection

Data collected for all subjects enrolled in this study should include the tests and procedures listed in the following Schedule of Activities (Table 1), many of which are part of routine data collection for all endovascular robotic procedures.

Table 1: Schedule of Activities

	Pre-Procedure	Procedure	Post-Procedure	90-day[7] ***BY PHONE***	180-day	Un-Scheduled Visit
		Day (0)	(24-hours post-procedure or hosp. discharge)	±14-days	±30-days	
Patient Eligibility Criteria	X					
Submit to Eligibility Committee • Clinical history • Unruptured Intracranial Aneurysm Treatment Score • Treatment plan • ≥ 4 angiographic (DSA or CTA/MRA) images	X					
Medical History	X[1]					
Digital Subtraction Angiography (DSA), Computed Tomography Angiography (CTA), or Magnetic Resonance Angiography (MRA)/Magnetic Resonance Imaging (MRI) of the brain/head	X[1]				X[7]	
Clinical assessment & Physical exam including: • Modified Rankin Scale (mRS) • National Institutes of Health Stroke Scale (NIHSS) scale	X		X	X[6]	X[8]	X[9]
Raymond Grade-Roy Occlusion Classification Scale	X[3]	X			X	
Laboratory Tests: hemoglobin, hematocrit, activated partial thromboplastin time, platelet count, international normalized ratio, pregnancy test, serum creatinine and glomerular filtration rate.	X[1,2,4]		X[2]			
Procedure Parameters		X				
Catheter Angiography		X[5]				
Contrast volume		X				
Record of AEs		X	X	X	X	X
Data for aneurysm assessment e.g. tortuosity, proximal & distal vessel diameter, target aneurysm measurements.		X			X	

[1] Within 7 days of index procedure.

[2] If performed under standard hospital procedure.

[3] For previously coiled aneurysms.

[4] Female subjects of child-bearing potential must have negative pregnancy test (urine or serum).

[5] Includes angiograms in the anterior posterior, lateral and working positions for analysis by a core laboratory.

[6] Telephone assessment and mRS is required. Other post procedure clinical assessment (scales/scores/grades) is left to the discretion of the investigator and shall be dictated by the patient's clinical symptoms.

[7] Post scans will be sent to the core laboratory for analysis.

[8] mRS is required. Other post procedure clinical assessment (scales/scores/grades) is left to the discretion of the investigator and shall be dictated by the patient's clinical symptoms.

[9] If visit is related to target aneurysm or potentially associated AE/SAE

5. ADVERSE EVENTS AND COMPLICATIONS

Throughout the course of the clinical investigation, all adverse events will be recorded on the applicable **ADVERSE EVENT** CRF and in the subject's medical records. In this study, adverse events will be defined and classified per ISO 14155:2020(E) Clinical Investigations of Medical Devices in Human Subjects - Good Clinical Practice, and as further described in this protocol. The date of onset, date of resolution, severity, and action taken will be evaluated by the Investigator. The relationship to the device, relationship to the procedure, and clinical significance will be evaluated. The neurological outcomes and adverse events will be reported.

5.1 Adverse Event Classification and Definitions

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device (ISO 14155:2011).
NOTE 1: This definition includes events related to the 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 medical devices.

Disease signs and symptoms that existed prior to study participation are not considered AEs unless the condition recurs after the subject has recovered from pre-existing condition, or the condition worsens in intensity or frequency during the study.

A Serious Adverse Event (SAE), as per the European Standard ISO 14155:2020(E), is an AE that led to any of the following:

a) Death
b). Serious deterioration in the health of subject, users or other persons as defined by one or more of the following:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or body function including chronic diseases, or

3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness of injury, or permanent impairment to a body structure or body function,

c) Foetal distress, foetal death, a congenital abnormality or birth defect including physical or mental impairment.

Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

In the current study indication, examples of a Serious Adverse Event (SAE) are:

- Incidence of death 24-hours post procedure
- Target aneurysm rupture
- Vessel perforation
- Vessel dissection
- Thromboembolic complication
- Failure to navigate to target
- Device failure to respond to input, or other intra-operative device failure

5.2 Adverse Event Assessments

Relatedness:

- Procedure-related: Event has a strong temporal relationship to the study procedure. This includes AEs attributable to any device(s) used at procedure, such as access devices, delivery microcatheters, embolic coils, non-ionic contrast, guidewires, or any other adjunctive, approved/cleared device for treatment of intracranial aneurysms.
- Device-related: Event has a strong temporal relationship to the CorPath GRX System.
- Unknown: Event relationship cannot be attributed to any of the above categories and remains undetermined.

5.3 Procedure-Related Adverse Event

An adverse event is procedure-related when, in the judgment of the Investigator; it is reasonable to believe that the event occurs from the endovascular robotic procedure, irrespective of the device.

5.4 Device-Related Adverse Event

An adverse event is device-related when, in the judgment of the Investigator, the clinical event has a reasonable time sequence associated with use of the CorPath GRX System and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the CorPath GRX System directly caused or contributed to the adverse event.

5.5 Event Reporting Requirements

Any adverse event that occurs during the course of the study must be recorded and reported using the appropriate **Adverse Event** eCRF and also recorded in the subject's medical records. These will include events occurring from the point of consent until a subject exits the study. The Investigator must sign each AE eCRF report. Investigators must obtain all information available to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as serious and the relationship of each adverse event to the procedure or device. This determines whether it requires notification to the Sponsor, regulatory agency, and as applicable, EC, within the specified reporting timeframe. AEs will be categorized using the definitions in Section 5.1 – 5.4.

Pre-existing medical conditions or symptoms occurring prior to the start of the procedure should not be reported as adverse events. In the situation where there is a worsening of a pre-existing medical condition or symptom due to a study related procedure, an adverse event should be reported.

In the case of any **AE**, the Investigator shall submit to Corindus a report *within 10 working days after the Investigator first learns of the event*.

The Investigator is required to report all SAEs within 24-hours after first learning of the event to

the Sponsor. The primary method of reporting SAEs will be through the eCRFs. If the database is unavailable, the investigator may fax or email in the information. As soon as the database becomes available, the investigator must complete data entry. Depending upon the nature and seriousness of the adverse event, the Sponsor may request the Investigator to provide anonymous copies of the subject's available supporting documentation (such as the subject's laboratory tests, hospital records, discharge reports, autopsy reports, Investigator summaries, etc.) to document the adverse event. The Sponsor is responsible in Europe for ensuring that the required and adequate information concerning the reported SAE is relayed to the appropriate Ethics Committee and Competent Authority using the MEDDEV 2.7/3 SAE Report Table. All other adverse events (i.e. other than serious adverse events) must be recorded on the appropriate adverse event eCRF.

Corindus, in cooperation with the Investigator, will assess all serious adverse events for potentially reporting to the Regulatory Authorities and EC.

For any adverse event that is ongoing at the time of the initial report, periodic follow-up information is required until the adverse event is resolved or is judged to be chronically stable, or until the conclusion of the study for the subject. The site should submit relevant follow-up information related to the adverse event as soon as it is available.

5.6 Anticipated Adverse Events

There are risks associated with endovascular embolization with or without stent-assist coiling procedure to treat cerebral aneurysms. These standard risks may include the following:

- Adverse reaction to antiplatelet/anticoagulation agents or contrast media
- Air embolus
- Allergic reaction/toxic effects
- Bleeding
- Death
- Device migration or misplacement
- Device Fracture
- Dissection of the parent artery
- Embolism
- Fever
- Foreign material embolic event
- Groin injury

- Headache
- Hemolysis
- Hemorrhage
- Hydrocephalus
- Infection
- Intracerebral bleeding
- Ischemia
- Neurological deficits
- Occlusion of unintended vessel
- Parent Artery Stenosis
- Perforator occlusion
- Peripheral embolism
- Post-procedure bleeding
- Ruptured or perforated aneurysm
- Recanalization
- Residual flow
- Seizure
- Stroke/TIA
- Surgical intervention
- Thromboembolism
- Vascular access site complication
- Vasospasm
- Vessel perforation
- Vessel trauma/perforation/occlusion
- Vision impairment

5.7 Subject Death

Subject death during the investigation must be reported via eCRF within 24-hours of Investigator's knowledge of the death. Notification of death must include a brief statement of the relevant details of the death and is required to be signed by the Investigator. In addition, all patient deaths must be reported to the specific Ethics Committee and Competent Authority in accordance with regulatory requirements. The method of declaration will conform to the current regulations. A copy of the death records, death certificates and an autopsy report (if performed) are required to be sent to Corindus or designee, within ten (10) days following the death.

In the event of subject death, efforts should be made to perform an autopsy in order to assess the state of the heart. For subjects that do not undergo autopsy, written documentation from the Investigator will be required providing justification as to why an autopsy was not performed.

5.8 Surveillance Committee

A Surveillance Committee will be composed of three expert physicians in the field of interventional neuroradiology and/or neurosurgery, who are independent and not directly involved in the conduct of the trial. The purpose of the committee is to review and adjudicate all complications/adverse events as they occur over the course of the study (classify, identify causal relationship between event and device, procedure or subject). The committee will also review and adjudicate, as necessary, issues relating to classification of events as major (serious) or minor (non-serious), and attribution to system, treatment and/or disease. The neurological outcomes and adverse events will be reported under the clinical investigation and any imaging generated will be forwarded to the committee. The committee will analyze the relationship between the images and the cause of the neurological deterioration. Any overall trends or conclusions drawn from these analyses will be reported; however, no specific criteria will be applied.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS

Data for subjects that undergo an endovascular procedure where the Corindus GRX device is used (or attempted to be used) will be included in both primary and secondary endpoints where data are available.

6.1 Analysis of Primary Effectiveness Endpoint

The primary effectiveness endpoint will be defined as successful completion of the robotic-assisted endovascular procedure absent any unplanned conversion to manual operation for guidewire, microcatheter, embolization coil(s), intracranial stent(s), or inability to navigate vessel anatomy. The proportion of subjects with a successfully completed endovascular procedure will be summarized along with a 2-sided 95% exact binomial confidence interval to demonstrate that the effective-ness is not inferior to a performance goal based upon historical rates from recent literature for comparable procedures.

6.2 Analysis of Primary Safety Endpoint

The primary safety endpoint will be a composite of intra- and peri-procedural events, including target aneurysmal rupture, vessel perforation or dissection, and major stroke within 24-hours of post-procedure or discharge, whichever occurs first. The proportion of subjects with a safety event as defined will be summarized along with a 2-sided 95% exact binomial confidence interval to demonstrate that safety not inferior to a performance goal based upon historical rates from the literature for comparable procedures.

6.3 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed with descriptive statistics along with a 95% confidence interval. Descriptive statistics for categorical variables will include the number and percentage of subjects in each category, with two-sided 95% confidence intervals of the percentage of subjects in each category. Descriptive statistics of continuous variables will include sample size, mean standard deviation, minimum, median, maximum, and 95% confidence interval of the mean. Summaries will be provided for the overall population and by type of aneurysm (ruptured or unruptured).

6.4 Determination of Historical Controls

Safety rates from key literature are presented in Table 2 below:

Table 2. Rates of safety from literature for endovascular treatment of unruptured and ruptured aneurysms.

	N Aneu-rysms (Pts)	Mortality at Discharge	Overall Complication Rate	Rupture/ perforation Rate (%)	Embolism Rate (%)
UNRUPTURED INTRACRANIAL ANEURYSMS					
Algra et al 2018*	**73066 (71819)**	**0.3% (0.2% - 0.4%)**	**4.96% (4.00, 6.12%)**	**0.9% (212/18520) 95% CI (0.6%, 1.3%)**	**2.82% (437/16000) 95% CI (2.3, 3.5%)**
*Advanced Endovascular Methods***	*2248*	*0.4%* *(0.2 - 1.1%)*	*6.1%* *(4.3, 8.7%)*		
Kawbata et al 2017	**1406 (1375)**			**1.4% (20/1406)**	
coil only	*340*			*1.8% (6/340)*	
stent-assisted coiling	*468*			*0.9% (4/468)*	
balloon-assisted coiling	*598*			*1.7% (10/598)*	
From Lit Review, Table 6 in Kawbata	***7785***	***0***		***1.4% (108/7785)***	
Zheng et al 2016	*1127*			*1% (11/1127)*	
Santillan et al 2013	*217*	*0%*		*5% (3/217)*	
Shigematsu et al 2013	*4767*			*1.4% (65/4767)*	
Oishi et al 2012	*500*	*0%*		*1.4% (7/500)*	
Im et al 2009	*435*	*0%*		*0.9% (4/435)*	
Pierot et al 2008	*739*	*0.3%*		*2.4% (18/739)*	
Pierot et al 2008 **(ATENA study)**	**739 (649)** **(700 procs)**	**1 month 1.4%**	**15.4%**	**2.4% (18/739)** **2.6% (18/700)**	**7.3% (29/308)** **7.1% (per proc)**

	N Aneurysms (Pts)	Mortality at Discharge	Overall Complication Rate	Rupture/ perforation Rate (%)	Embolism Rate (%)
Pierot et al 2009, (ATENA study, coil alone results)	325 pts	0.9% (3/325)	10.8% (35/325)	2.1% (7/325)	6.2% (20/325)
RUPTURED INTRACRANIAL ANEURYSMS					
Zhang et al 2019	1004	All cause 9.5% (5.8%, 13.2%) proc related 1.8% (0.9, 2.7%)	22.7%*** 95% CI (15.1, 30.3%)		
Cognard et al 2011 (CLARITY GDC study)	405	1.50%		3.7% (15/405)	13.3% (54/405)
Pierot et al 2011 (CLARITY)	608	5.1% (31/608) cum. TRT related morb/mort rate 19.6% (119/608) cum. morb/mort rate)	17.4% (106/608)	4.6 (28/608)	

*** rates presented are pooled crude risk from meta-analysis modeling**
**** Advanced = Stent-assisted coiling, balloon-assisted coiling, flow diverting stents or woven endo-bridge devices.**
***** definition not specified**

Additionally, there were three randomized controlled trials comparing different endovascular treatments that contained both ruptured and unruptured intracranial aneurysms: HELPS, MAPS, and Cerecyte Coil trial. Rates presented pooled results from both arms in the following three tables.

Table 3a-3c. Rates presented pooled results from both arms from three (3) from randomized control trials.

HELPS Trial	N	Mortality	Procedural aneurysm rupture*	Thromboembolic complication*
White et al 2008 N=499 RCT, covered vs uncovered coil 53% ruptured	499	2.2% (11/499) At dis-charge	3.4% (17/499)	9.8% (39/499)

* Article specifically called out that "some of these adverse events, especially procedural ones, did not result in permanent clinical sequalae.

MAPS Study	N	Mortality	Overall Complica-tion Rate	Clinical Event Committee Adjudicated			Technical Success
				Rupture/ re-rupture	Ischemic Stroke	Hemorrhagic Stroke*	
McDougall et al 2014 N=626 RCT, Matrix coil vs GDC coil Ruptured 36.4% (22826)	626	0.2% (1/624) Peri-proc 2.4% (15/626) 30 day	14.9% (93/624)	0.3% (2/626)	3.4% (21/626)	1.1% (7/626)	97.1% (608/626)

*Article notes hemorrhagic strokes due to rupture/re-rupture are not included in Hemorrhagic Stroke summary

CERECYTE Coil Trial	N	Mortality	Overall Complication Rate	Rupture/ re-rupture	Thrombo-embolic complica-tion	Neuro-deterio-ration	Technical Success
Coley et al 2012 N=500 RCT, Cerecyte vs bare platinum coil Ruptured 46.9% (233/497)	497	0% within 24-hr 0.4% (2/497) before dis-charge	12.3% (61/497)	3.6% (18/497)	5.6% (28/497)	3.0% (15/497)	97.2% (483/497) (14 "unable to place coil")

While Cerecyte and HELPS present overall complication rates in the 12-15% range, it was felt that the rates of stroke, rupture/re-rupture and death from the MAPS trial that were adjudicated by an independent clinical event committee were the most accurate to represent the expected rates of safety events for this trial. If we assume independence and add the individual rates, the

expected rate of safety events is 4.8% (30/626) but will be rounded to the nearest percent of 5% for sample size calculations.

The performance endpoint is similar to a technical success measure. Zang *et al* 2019 provided a literature review that included technical success. The weighted average was 97.6% for ruptured aneurysms. McDougall *et al* 2014 reported a similar overall procedural success of 97.1% (608/626) and Coley *et al* 2012 report a success of 92.7%, but this number does not include conversion to manual as our performance endpoint does.

For the conversion to manual aspect, there are not data available for treatment of intracranial aneurysms, but we can look at past Corindus CorPath performance for PCI. In Table 4 below, the premarket trial results 1.2% for unplanned conversions, but the rate was considerably higher in the real-world post-market trial with 10.4% unplanned conversions.

To estimate the overall rate of success for the performance endpoint, we will use the highest rate of 10.4% rounded to the nearest percent of 10%, or in terms of success, 90% expected performance success rate.

Table 4. Summary of conversion to manual by Corindus CorPath device in percutaneous coronary interventions.

Trial		Conversion to Manual
PRECISE	Pre-market trial for FDA clearance	1.2% (2/164)
PRECISION Registry*	Post-market trial	10.4% (99/948)
CORA-PCI	Post-market single site trial	8.3% (9/108)
* Unpublished data		

For a few secondary endpoints intending to quantify performance at 180 days, safety and effectiveness rates from a key publication (The Pipeline Trial) related to 180-day follow-up are presented in table 5[50].

Table 5. Safety and Effectiveness data 180-day rates presented.

Pipeline for Uncoilable or Failed Aneurysms Clinical Trial Becske et al 2013.[50]	**N**	**180-day Results (%)**
SAFETY		
• Ischemic stroke (perioperative) related to PED-associated thrombosis (patient later experienced delayed fatal hemorrhage after traumatic fall in rehabilitation facility)	107	2.8% (3/107)
• Ischemic stroke (delayed) secondary to major in-construct (PED) stenosis		---
• Ischemic stroke (delayed) from noncompliance with the required oral antiplatelet regimen		---
• Ipsilateral intraparenchymal hemorrhage (perioperative)		1.9% (2/107)
• Ipsilateral intraparenchymal hemorrhage (delayed) on day 14 (fatal)		---
• Rapidly fatal event possibly neurologic in origin		0.9% (1/107)
EFFECTIVENESS	**N**	**180-day Aneurysm**
• Angiographic evaluation that demonstrated complete aneurysm occlusion and absence of major stenosis at 180 days	106	
○ YES		73.6% (78/106)
○ NO		26.4% 28/106

The goal of the Pipeline trial safety analysis was to show the rate of ipsilateral stroke or neurologic death is statistically lower than 20%. The rate of complete aneurysm occlusion analysis goal was set at a threshold of 50%. The Pipeline trial demonstrates that treatment of large and giant cerebral aneurysms is feasible and effective, with a reasonable margin of safety. Patient follow-up for the trial consisted of repeat neurologic examinations at 30 and 180 days after device placement and a follow-up telephone call evaluation at 90 days. Further periodic follow-up visits were scheduled (through 5 years). Patients underwent conventional angiography and a neurologic examination at 180 days. In this study, the 180-day follow-up data imply that fewer angiographic follow-up visits are required.

6.5 Primary Analysis

The goal of the primary analysis will be to demonstrate that cerebral aneurysm coiling treated with CorPath GRX is as effective and safe as compared to the combined historical control treatments for cerebral aneurysm coiling treated with traditional manual operation.

For safety, if the upper bound of the 2-sided 95% confidence interval is less than the performance goal of 15%, we will conclude that the Corindus GRX system did not negatively impact safety.

For performance, if the lower bound of the 95% confidence interval for the proportion of successful patients is greater than the performance goal of 80%, we will conclude that the Corindus GRX system did not negatively impact performance.

6.6 Sample Size Calculation

Assuming that the expected safety for procedures performed with the Corindus GRX system do not differ from historical performance, we set up a performance goal using the historical rate of 5% for safety and an 10% non-inferiority margin to set up a performance goal of 15% for safety. The safety hypothesis is:

Ho: $p \geq 15\%$ (5% + 10% NI margin)

Ha: $p < 15\%$,

where p=proportion of patients with a safety event.

A sample size of 96 subjects will have at least 90% power to test this safety hypothesis (PASS 14, one-sample proportion, exact test, normal approximation for power).

Assuming that the expected procedure success rate is similar to the 90% based on literature and our best estimate of possible conversion to manual procedures, we set up a performance goal using the historical rate of 90% for with a 10% non-inferiority margin to set up a goal of 80% for performance.

The performance hypothesis is:

Ho: $p \leq 80\%$ (90% - 10% NI margin)

Ha: $p > 80\%$,

where p=proportion of patients with a successfully completed endovascular procedure.

A sample size of 108 subjects will have at least 80% power to test this safety hypothesis (PASS 14, one-sample proportion, exact test, normal approximation for power).

The overall trial sample size for the trial will be driven by the performance endpoint with at least 108 subjects enrolled.

6.7 Endpoint Analysis and Reporting

All statistical analyses will be performed using SAS Version 9.4 or higher or other valid statistical software. Descriptive summary statistics will be provided for endpoints along with 95% confidence intervals as appropriate. Subject data listings and tabular and graphical presentations (e.g., bar graphs, pie charts, line graphs) of results may also be provided.

The secondary endpoint at the nominal 90 days post-procedure (modified Rankin Score) will be reported with descriptive statistics. Secondary endpoints captured at the nominal 180-day visit will be presented in tabular format (see Table 5) where appropriate; and for Clinical assessment & Physical Exam variables, with descriptive statistics; data for Target Aneurysm Assessment will be presented in a tabular format (see Table 1).

Adverse events occurring during or before the post procedure visit identified in Table 1 will be reported separately. Adverse events occurring after this visit will be reported (1) separately and (2) pooled with prior adverse events.

An analysis of periprocedural data will be performed upon completion of the post-procedure visit of the 108th enrollment and/or enrollments that have closed. The final analysis will be performed after follow-up is completed for all enrolled subjects. A separate statistical analysis plan (SAP) will be prepared and will include additional details for planned analyses.

6.8 Analysis of Baseline Demographics and Procedural Characteristics

All clinically relevant baseline variables will be tabulated using descriptive statistics.

6.9 Handling of Missing Data

It is assumed that because the primary and most secondary analyses are evaluated within 24-hours of CorPath GRX procedure or prior to hospital discharge, whichever occurs first, there will be minimal missing data. For the 90-day and 180-day secondary endpoints (modified Rankin Scale, thromboembolic events, and aneurysm occlusion), all practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. Additionally, all data collected on safety or adverse events will be reported to the extent they are available.

7. DATA COLLECTION

7.1 Study Data Requirements

To ensure data quality and completeness, all required data will be recorded on standardized electronic case report forms (eCRFs). eCRFs must be completed for each subject and, once complete, electronically signed by the Investigator in the electronic data capture (EDC) system. The Investigator will electronically sign after all data has been entered, all queries have been resolved, and all monitoring is completed. The Investigator, or their authorized designee, is responsible for recording all study data in the eCRFs. If a paper CRF is used to capture any additional study related data, it must be signed and dated by the Investigator.

7.2 Data Processing & Quality Control

A full-featured relational database on a central server, networked to data entry and data analytical workstations will be employed. Conventional data verification sub-routines will be extensively programmed to test entry and logical errors, while all individual (subject based) case report forms will be linked for cross-reference. Periodic analysis of each data field (a cross cases) will be performed to examine the expected distributions of data, and to identify outliers for possible data mistakes.

7.3 Data Cleaning

All eCRFs will be subjected to inspection for completeness, data inconsistencies, clarity and deviations upon receipt. All deficiencies or deviations will be reported to the site as necessary. All data inconsistencies will be resolved with the revision of errant forms at the clinical site, by site

personnel.

7.4 Data Entry

Study data will be collected using electronic case report forms and a 21 CFR Part 11-compliant electronic data capture system. Part 11, Title 21 of the US FDA's Code of Federal Regulations (CFR), or FDA 21 CFR Part 11, is particularly important because it details the regulations for the use of electronic documents and signatures. The application provides the capability of data collection remotely through the Internet so the participating site personnel may log on the system securely and enter the data. All subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and investigation-specific data entry conventions for data accuracy and logical meaningfulness. Periodic analysis of all subjects' collected data will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors. The investigator is responsible for reviewing all eCRF entries for completion and correctness. Changes in case report forms will be made electronically and the system used will keep an audit trail of changes. If necessary, an explanation for the change(s) may be provided. All study staff who will enter data into eCRFs will undergo appropriate training for use of electronic CRFs. Further information regarding eCRF navigation and use may be found in the eCRF Completion Guidelines.

7.5 Final Data Analyses

All exported datasets for analyses will undergo a final data cleaning procedure unique to each exported dataset.

7.6 Confidentiality and Protection of Study Files

Information about study subjects will be kept strictly confidential, including their personal identity and all personal medical information. Subjects will be identified by a unique study number consisting of site number – subject ID number. The patient's consent to the use of records for data verification purposes will be obtained prior to enrollment in the trial.

The Investigator Site File will be held in a secure area. Only personnel responsible for collecting the data and transcribing it onto the case report forms will have access to the data. Records will remain on site in secure areas.

Appropriate precautions will be taken to maintain confidentiality of subject medical records and personal information. However, the subject's name may be disclosed to the Sponsor, Corindus, or health authorities if they inspect the clinical investigation records. A report of this clinical investigation may be published; however, the subjects' identities will not be disclosed.

Passwords will be issued to appropriate site, monitoring and Sponsor personnel to ensure confidentiality and protection of the data by allowing variable levels of access to the computer system. All data collection and reporting will follow strict adherence to the US Health Insurance Portability and Accountability Act (HIPAA) and EC guidelines for subject confidentiality.

7.7 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, X-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The site will make available all source documents for inspection.

The following information should be included in the subject's medical record:

- Subject's name and contact information
- The fact that the subject is participating in an approved clinical investigation
- The clinical investigation title and reference number
- The date the subject was enrolled into the trial and the subject ID number
- A statement that written informed consent was obtained;
- Date of procedure and device lot number;
- Dates of all visits;
- Lists of medications;
- Documentation of Adverse Events;
- Date subject exited the clinical investigation, and a notation as to whether the subject

completed the clinical investigation or discontinued, with the reason for early termination.

7.8 Record Retention

In order to constitute evidence with respect to product safety or regulatory or legal compliance, the Investigator agrees to retain clinical investigation-related documents in a location that is secure and to which access can be gained if required. The following documents must be archived: Investigator's File containing all regulatory agency and required GCP documents, including, for example, signed Patient Informed Consent forms and subject-related materials, CRFs, and Data Clarification forms.

Documents should be retained by the Investigator for the appropriate period (i.e., 15 years in Europe or according to the local country regulations).

All clinical investigation-related correspondence, subject records, consent forms, records of the distribution and use of the investigational products, and copies of eCRFs should be maintained on file. Corindus requires notification in writing if the Investigator wishes to relinquish ownership of the data so that mutually agreed upon arrangements can be made for transfer of ownership to a qualified entity.

8. MONITORING PROCEDURES AND AUDITING

The study site will be monitored to ensure that the study is conducted in full compliance with the CorPath GRX Neuro Study protocol and GCP.

The site initiation visits will include, but is not limited to:

- Training in adherence to GCP
- Review of the clinical protocol
- Training on techniques for the identification of eligible subjects and in-hospital data collection
- Data collection
- Training on the proper and timely reporting of AEs
- Use of the electronic data capture (EDC) system and eCRF completion

8.1 Study Monitoring Plan

Data from all investigational sites will be monitored as it is submitted to the Sponsor. Qualified employees of the Sponsor, or a qualified contract research organization (CRO) under contract with the Sponsor, will conduct periodic monitoring visits to perform source data verification, evaluate protocol compliance, and determine if there are any issues that could affect the safety or welfare of any subjects in the study.

The Investigator will make subject and other study records available to the study monitor for periodic inspection, according to the Sponsor's clinical monitoring procedure. The monitor will perform periodic on-site visits. These visits will be done prior to enrollment of the first subject and at intervals during the course of the study. The investigational site will allow the monitor access to thee CRFs and supporting source data (unless prohibited by national law). The monitor may also perform on-site review of medical records if there is a subject death, any unanticipated adverse events, or higher frequency of adverse events than expected.

The study monitor is responsible for the conduct and administration of this clinical study. These responsibilities include maintaining regular contact with each investigational site and conducting on-site monitoring visits at each investigational site to ensure compliance with this Investigational Plan; to verify that accurate and complete data are being submitted in a timely manner; and to verify that the investigative site facilities continue to be adequate. Concerning completed eCRFs for all study patients, the monitor will perform 100% source document verification for all subjects.

The name and address of the Corindus Study Director is:

Tina Ridgeway
Corindus Clinical Research Manager
Corindus, Inc.
309 Waverley Oaks Road, Suite 105
Waltham, MA 02452
USA
tina.ridgeway@corindus.com

The Corindus Study Director will:

- Oversee performance of CRO (if contracted) including monitoring, to ensure compliance

with study protocol; and in accordance with scope of work and in accordance with Good Clinical Practice.

- Resolve patient eligibility and protocol deviation issues.
- Review monitoring reports for accuracy, completeness and conformance with SOPs.
- Maintains frequent contact with and work effectively with Investigators and coordinators.
- May monitor/audit clinical sites for adherence to protocol, GCP, including conducting site pre-qualification, initiation, monitoring visits, and close-out visits or co-monitoring visits conducted by CRO personnel.
- Assurance of regulatory compliance of investigational sites with company SOPs and ICH guidelines.
- Perform clinical data review of data listings and summary tables, including query generation.
- Review and/or submission of research Ethics Committee/Regulatory documentation.
- Identify, select, and monitor performance of investigational sites for clinical studies; prepare accurate and timely visit reports from all site interaction visits.

8.2 Monitoring Responsibilities

Monitoring responsibilities performed by Corindus or its designees include, but are not limited to the following:

- Site initiation visits;
- Interim monitoring visits to:
  - Assess protocol compliance;
  - Conduct source document verification;
  - Assess case report forms accuracy and completeness;
- Telephone contacts with site;
- Maintenance of records of Investigator/monitor contacts;
- Final site close-out visit.

The study monitor is responsible for the conduct and administration of this clinical study. These responsibilities include maintaining regular contact with each investigational site and conducting on-site monitoring visits at each investigational site to ensure compliance with this Investigational Plan; to verify that accurate and complete data are being submitted in a timely manner; and to verify that the investigative site facilities continue to be adequate. Concerning completed eCRFs

for all study patients, they will be reviewed for accuracy during these visits and the monitor will perform 100% source document verification for all subjects. The trial progress will be discussed with the Investigator.

8.3 Protocol Deviations

A protocol deviation is a failure to comply with the requirements of the clinical study as specified in the protocol. Examples of protocol deviations include late visits, required follow-up testing not completed, or enrollment of a study subject who fails to meet inclusion/exclusion criteria as specified in the protocol. Each Investigator shall conduct this clinical study in accordance with the study protocol and any conditions required by the reviewing Ethics Committee and Competent Authority.

Deviations from clinical protocol requirements will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective actions put into place. Corindus accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well-being of a study subject. The Investigator must give notice of any emergency deviations and justification for the deviation to Corindus as quickly as possible after the episode, in any event no later than 24-hours after the emergency. Corindus will report all deviations to the Ethics Committee and Competent Authority.

8.4 Protocol Changes

The Investigator should not implement changes to the protocol without prior approval by Corindus and prior review and documented approval from the governing Ethics Committee and Competent Authority. The only exception to this requirement is the necessity to eliminate immediate hazards to subjects in the clinical investigation, or when changes involve only administrative aspects (e.g., change in monitors, telephone numbers, etc.).

Any report of withdrawal of Ethics Committee or Competent Authority approval will be submitted to the Sponsor.

8.5 Auditing and Regulatory Inspections

The site will permit study-related monitoring, audits, and inspections by the Sponsor and government regulatory bodies of all study related documents (e.g., source documents, regulatory

documents, data collection instruments, study data, etc.). The site will ensure the capability for inspections of applicable study-related facilities (e.g. interventional/surgery center, imaging facilities, etc.).

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices. Each Investigator is required to execute an Investigator Agreement which delineates their responsibilities in this regard.

It is important that the Investigator and relevant study personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

9. DATA QUALITY ASSURANCE

9.1 Adverse Event Handling

The Sponsor will identify events associated with the study endpoints and additional event review may be performed, as described below. Clinical sites will follow their routine hospital procedures for adverse event handling, as necessary.

9.2 Study Endpoint Event Adjudication

A site independent review of all clinical events associated with the study endpoints will be conducted. Adjudication will be based on narratives and source data supplied by the sites. Source data that may be collected for review include, but are not limited to, de-identified procedural angiograms, endovascular lab report, procedure report, discharge summary and lab reports. The sites may be contacted for queries and additional support documentation.

10. SITE AND INVESTIGATOR SYSTEM TRAINING

Both Investigators and clinical staff will undergo a comprehensive CorPath GRX System training to ensure they are ready to perform robotic procedures prior to enrollment into the study. Training will be per the CorPath GRX System Operator's Manual.

10.1 Site Training

All clinical site personnel participating in robotic endovascular procedures will successfully complete the CorPath GRX System training program. The site training will be conducted by Corindus or their representatives. All clinical staff training will be documented.

10.2 Investigator Training

CorPath GRX System should only be used by qualified personnel familiar with endovascular procedural techniques. Each Investigator will successfully complete the CorPath GRX System training program (which includes didactic and hands-on sessions with the CorPath GRX System) prior to subject enrollment. Training will be conducted by Corindus or their representatives. All Investigator training will be documented.

11. ADMINISTRATIVE RESPONSIBILITIES

The CorPath GRX Neuro Study will be conducted in accordance with GCP including the study protocol, the fully executed Clinical Study Agreement and all applicable regulations.

11.1 Ethical Considerations

This study will be conducted as a Post-Market study. The study will be conducted according to Good Clinical Practice (GCP) guidelines; with informed consent and independent Ethics Committee review and approval as defined in the World Medical Association Declaration of Helsinki, Competent Authority review and approval (if applicable), ISO 14155:2020(E) and the Medical Device Regulations (2017/745) of 5 April, 2017.

This protocol and any amendments will be submitted to a properly constituted Ethics Committee and Competent Authority (if applicable) for formal approval of the study conduct. The decision of the Ethics Committee and Competent Authority (if applicable) concerning the conduct of the study will be made in writing to the Sponsor and a copy of this decision will be provided to the Investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this

study. This document will be submitted with the protocol for review and approval by the Ethics Committee for the study and the Competent Authority (if applicable). The formal consent of a patient, using the EC-approved consent document must be obtained before that patient undergoes any study procedure. The consent document must be signed by the patient and the Investigator-designated research professional obtaining the consent. The Investigator will retain a copy of the signed informed consent document in each subject's record and provide a copy to the subject.

Although not indicated in the Patient Information Sheet, in certain countries the Ethics Committee requires that all subjects included in the clinical investigation must be affiliated with their respective national social security system. It is up to the investigator to find out if the subject has this required affiliation.

11.2 Confidentiality

All data sent to Corindus or their authorized designee, concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject.

11.3 Study Registration and Publication

The CorPath GRX Neuro Study will be registered with ClinicalTrials.gov prior to the start of enrollment. ClinicalTrials.gov is a registry of clinical trials and is a publically accessible database. It is run by the United States National Library of Medicine (NLM) at the National Institutes of Health, and is the largest clinical trials database in the world. The results of the clinical investigation will be made publically available.

Corindus, as the Sponsor, has a proprietary interest in this clinical investigation. Authorship and manuscript composition will reflect joint cooperation between the Investigator, clinical investigation site, and Corindus. Authorship will be established prior to writing of the manuscript. No individual publications will be allowed prior to the completion of the final report for this clinical investigation and as agreed in writing by Corindus.

A *Publications Committee* will be formed to review and publish the data from the clinical investigation. This committee will consist of investigators and representatives of Corindus. The

Publications Committee will write/review all drafts of abstracts, full-length manuscripts and/or oral congress presentations/posters and will choose the appropriate journal (for manuscripts) or meetings (for abstracts) for submission.

The "Coordinating" Principal Investigator will submit copies of proposed materials to Corindus prior to submission for publication or presentation. Corindus will have an appropriate period of time for review.

Corindus reserves the right to delete any confidential information or other proprietary information from the proposed publications or presentations.

The Principal Investigator will properly acknowledge Corindus in all publications or presentations resulting from the clinical investigation. Corindus will have the royalty-free right to reproduce, translate, and use publications and presentations for any and all purposes. Written permission must be obtained from the Principal Investigator or Corindus to use the other's name in any form of publicity.

11.4 Angiographic Core Lab

The following assessments will be made by the Angiography Core Lab from images submitted from the sites. The procedural angiograms will be submitted by site with all subject identifiers removed and only the assigned subject study number on the images.
Procedural, pre, peri and post images:

- Aneurysm location
- Raymond-Roy Occlusion Classification grade (pre-procedure required only for previously coiled aneurysms)
- Stenosis of parent and branch arteries(pre-procedure)

12. FUNDING

This clinical investigation is funded by Corindus, Inc.

13. DEFINITIONS

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.
Device-Related Adverse Event	Event has a strong temporal relationship to the study device, and alternative etiology is less likely.
Major Stroke	A stroke, which increases the NIHSS of the subject by ≥ 4.
Minor Stroke	A stroke, which increases the NIHSS of the subject by ≤ 3
Transient Ischemic Attack (TIA)	A transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction.
Modified Rankin Scale (mRS)	Scale for measuring general neurologic function. 0. No symptoms at all 1. No significant disability despite symptoms; able to carry out all usual duties and activities 2. Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3. Moderate disability; requiring some help, but able to walk without assistance 4. Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5. Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6. Dead
NIHSS Scale	The National Institutes of Health Stroke Scale, or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment.[1]The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0
Neurological Deterioration	Defined as ≥ 4-point increase compared with baseline in the NIHSS at discharge.
Procedural Related Adverse Event	Defined as events that occur from the endovascular robotic procedure, irrespective of the device.

Raymond-Roy Occlusion Classification Scale	Angiographic classification tool for grading occlusion of aneurysms treated with embolization.
	• Class I: Complete Obliteration
	• Class II: Residual Neck
	• Class III: Residual Aneurysm
	  ○ Class IIIa: contrast opacification within the coil mesh
	  ○ Class IIIb: contrast opacification outside coil mesh

Screen Failure	A subject who signs an informed consent form (ICF) and does not have a CorPath GRX endovascular procedure or is enrolled in the study but withdraws their consent.

Serious Adverse Event	All Serious Adverse Events are defined as an adverse event where the outcome is one of the following: 1. Death 2. Life-threatening, where the patient was at substantial risk of dying or continued use of product might have resulted in death 3. Hospitalization or prolongation of an existing hospitalization 4. Disability or permanent damage, interfering with the patient's ability to conduct normal life functions 5. Congenital anomaly or birth defect 6. Required intervention to prevent permanent impairment
Stroke	A focal neurological deficit of presumed vascular origin persisting more than 24-hours from symptom onset AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. The 24-hour criterion is excluded if the subject undergoes cerebrovascular surgery or dies during the first 24-hours of symptom onset. The definition includes subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. The definition also includes sudden loss or worsening of visual acuity due to retinal artery occlusion or retinal emboli. The definition excludes slowly progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth. The definition also excludes stroke events in cases of blood disorders such as leukemia or external events such as trauma. Stroke severity will be graded by the Investigator as major or minor: • Major Stroke: A stroke which increases the NIHSS of the subject by ≥4. • Minor Stroke: A stroke, which increases the NIHSS of the subject by ≤3. • TIA: a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction

14. STUDY ADMINISTRATIVE STRUCTURE

Please refer to Appendix A for names of Investigators, Sites and the study Administrative Structure.

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APPENDIX A INVESTIGATORS, SITES AND ADMINISTRATIVE STRUCTURE

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APPENDIX B REVISION HISTORY

Version	Version Date	Summary of Changes
A	**October 15, 2019**	• **Initial release**

A.1	**October 18, 2019**	• **Summary**
		  • Clarified investigational site information
		  • Clarified inclusion criteria
		  • Updated secondary endpoints
		• **Schedule of Activities**
		  • Removed complete blood count and platelet function testing
		  • Added hematocrit (HCT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR)
		• **Section 3.4 Secondary Endpoints**
		  • Removed Operator Radiation Exposure and renumbering of secondary endpoints
		• **Section 4.6 Inclusion Criteria**
		  • Clarification of robotic assisted endovascular treatment
		• **Section 4.8.2 Baseline Data**
		  • Removed complete blood count and platelet function testing
		  • Added hematocrit (HCT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR)
		• **Section 4.8.4 Data Collection During CorPath Procedure**
		  • Removed Operator Radiation Exposure
		• **Section 4.8.11 Schedule of Data Collection**
		  • Removed complete blood count and platelet function testing
		  • Added hematocrit (HCT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR)
		• **Appendix A**
		  • Added an additional Study Center
		• **Updated general protocol formatting**

Rev. B	**October 31, 2019**	• **Section Study Summary**
		  • Added that each site will recruit approximately 20 subjects
		  • Address change for Alan Cohen, Monitoring Services
		• **Schedule of Activities**

		• Clarified post procedure clinical assessment (scales/scores) is left to the discretion of the investigator • **Section 4.1 Overview of Trial Design** • Added each site will recruit approximately 20 subjects • **APPENDIX A - INVESTIGATORS, SITES AND ADMINISTRATIVE STRUCTURE** • Address change for Alan Cohen, Monitoring Services
Rev. C	**December 12, 2019**	**ONLY FOR CANADA** • **Section Study Summary** • Changed Site Investigator to Coordinating Principal Investigator • Added Local Site Principal Investigator – Dr. Vitor Pereira
Rev. D	**January 31, 2020**	• **Section Study Summary** • Dr. Piotin is now the "Study" Coordinating Principal Investigator • Modified inclusion criteria #4 • Added inclusion criteria #5 • Modified exclusion criteria #1 • Added exclusion criteria #2 and #4 • **Section 4.4 Informed Consent Procedures** • Added that subject will have at least 24 hrs to consider participation in the study. • Added that this consent shall be obtained from each "conscious" subject prior to the investigational procedure. • Added that in the case of an unconscious subject due to a ruptured cerebral aneurysm where emergency intervention is required, a family member may sign the patient consent form for inclusion in the study. If and when the subject recovers and is conscious, the subject is required to sign the patient consent form. • **Section 4.6 Patient Selection** • INCLUSION Criteria ▪ Modified for #4: The "conscious" subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent. ▪ Added criteria #5: In the case of an

		unconscious subject due to a ruptured cerebral aneurysm where emergency intervention is required, a family member may sign the patient consent form for inclusion in the study. • EXCLUSION Criteria ▪ Modified for #1: "For a conscious subject, failure / unwillingness" to provide informed consent, unless the EC has waived informed consent. ▪ Added criteria #2: In the case of an unconscious subject due to a ruptured cerebral aneurysm, a family member may sign the patient consent form for inclusion in the study, however, if during the preliminary evaluation in the interventional suite the subject's anatomic conditions do not meet the selection criteria, the subject will be excluded from the study. ▪ Added criteria #4: Women who are pregnant and persons under guardianship or curatorship. • **Appendix A** • Dr. Piotin is now the "Study" Coordinating Principal Investigator • Added to Study Centers Dr. Sourour (Paris, France), Dr. Galdamez (Valladolid, Spain), Dr. Holtmannspötter (Nürnberg, Germany), Dr. Gralla (Bern, Switzerland) and Dr. Brouwer (Leiden, Netherlands)
Rev. E	**February 28, 2020**	• **Appendix A** • Added to Study Centers Prof. Costalat (Montpellier, France)
Rev. F	**June 25, 2020**	**ONLY FOR CANADA** • **CORPATH GRX NEURO STUDY SUMMARY** • Added Secondary Endpoints ▪ Composite outcomes of procedure-related complications AND permanent focal neurological deficits assessed at 90-day and 180-day follow-up visits ▪ Aneurysm Occlusion Secondary Endpoint – changed duration from peri-

		procedure to post-procedure ▪ Expanded Core Laboratory secondary endpoint to include assessment at 180-day follow-up • **Schedule of Activities Tables** • Updated to reflect the addition of 90-day and 180-day follow-up • Added Telephone Assessment • **Section 3.4 Secondary End points** • Added secondary end point - Composite Outcomes of Procedure-Related Complications and Permanent Focal Neurological Deficits assessed at 90-day and 180-days • Aneurysm Occlusion Secondary Endpoint – changed duration from peri-procedure to post-procedure • Expanded Core Laboratory secondary endpoint to include Raymond-Roy Occlusion Classification at 180-days • **Section 4.8.5 Data collection Post Procedure** • Added NIHSS must be completed post procedure • Added recommended that telephone numbers and contact information be confirmed with the subject before discharge • **Section 4.8.11 Follow-up** • Added 90-day and 180-day follow-up assessment and testing requirements • **Section 6.4 Determination of Historical Controls** • Added new safety and efficacy data for 180-day follow-up • **Section 6.7 Endpoint Analysis and Reporting** • Adding secondary endpoint reporting for the 90-day and 180-day follow-up visits • **Section 11.4 Angiographic Core Lab** • Added 180-days ± 30 days post-procedure, assess Raymond-Roy Occlusion Classification • **Section 15 References** • Updated reference page • **Formatting changes**
Rev. G	**November 11, 2020**	**ONLY FOR CANADA → Rev F + Rev H combined**
Rev. H	**November 11, 2020**	• **Update ISO reference to ISO 14155:2020(E)**

		which became effective in July 2020
		• **Added specific section 2.2.4 (Device Accountability)**
		• **Section 4.1 (Overview of Trial Design) –** clarified
		• **Section 4.6 Patient Selection**
		  • INCLUSION Criteria
		  ▪ #2: removed ruptured intracranial aneurysms
		  ▪ #5: removed unconscious subjects
		  • EXCLUSION Criteria
		  ▪ #2: removed unconscious subject with a ruptured aneurysm
		  ▪ #4: clarified
		• **Added specific section 4.6.3 (Eligibility Committee)**
		• **Section 4.8.10 (Follow-up)** – clarified
		• **Section 5.1 (Adverse Event Classification and Definitions)** – updated to new ISO 14155:2020(E)
		• **Section 11.3 (Study Registration and Publication)** – clarified
		• **Appendix A (Investigators, Sites & Administrative Structure)** – updated

Rev. I	**May 21, 2021**	**All Sites**
		• **CORPATH GRX NEURO STUDY SUMMARY**
		  • Added Secondary Endpoints
		  • Composite outcomes of procedure-related complications AND permanent focal neurological deficits assessed at 90-day and 180-day follow-up visits
		  • Aneurysm Occlusion Secondary Endpoint – changed duration from peri-procedure to post-procedure
		  • Expanded Core Laboratory secondary endpoint to include assessment at 180-day follow-up
		• **Schedule of Activities Tables**
		  • Updated to reflect the addition of 90-day and 180-day follow-up
		  • Added Telephone Assessment
		• **Section 3.4 Secondary End points**
		  • Added secondary end point - Composite Outcomes of Procedure-Related Complications and Permanent Focal Neurological Deficits assessed at 90-day and

		180-days • Aneurysm Occlusion Secondary Endpoint – changed duration from peri-procedure to post-procedure • Expanded Core Laboratory secondary endpoint to include Raymond-Roy Occlusion Classification at 180-days • **Section 4.8.10 Data collection Post Procedure** • Added NIHSS must be completed post procedure • Added recommended that telephone numbers and contact information be confirmed with the subject before discharge • **Section 4.8.11 Follow-up** • Added 90-day and 180-day follow-up assessment and testing requirements • **Section 6.4 Determination of Historical Controls** • Added new safety and efficacy data for 180-day follow-up • **Section 6.7 Endpoint Analysis and Reporting** • Adding secondary endpoint reporting for the 90-day and 180-day follow-up visits • **Section 11.4 Angiographic Core Lab** • Added 180-days ± 30 days post-procedure, assess Raymond-Roy Occlusion Classification • **Section 15 References** • Updated reference page • **Appendix A** • Added to Study Centers Dr. Spears (Toronto, Canada) • Removed Dr. Manning (Liverpool, Australia), Dr. Holtmannspötter (Nürnberg, Germany) • Added Dr. Tomasello as Co-Principal Investigator to Barcelona, Spain • **Formatting changes**