Statistical Analysis Plan

For

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

Clinical Protocol Number: 104-08660

Version 4

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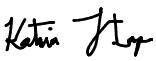
Katrina Harper	Statistician	 *Electronically signed by: Katrina Harper Reason: I have reviewed this document Date: Jun 21, 2022 10:42 CDT*	Jun 21, 2022

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1 Purpose

This Statistical Analysis Plan (SAP) is intended to provided additional details for planned summaries of the data in support of generating summaries and a final report for the clinical study, “An Evaluation of Effectiveness and Safety of the CorPath® GRX System in Endovascular Embolization Procedures of Cerebral Aneurysms”, clinical protocol number 104-08660, Rev F, I, and J.

2 Background

The Corindus CorPath GRX Neuro trial 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.

The CorPath GRX System is intended for use in the remote delivery and manipulation of interventional devices during percutaneous coronary and vascular procedures. 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 a bedside unit, interventional cockpit, and control console.

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 through180 days

The subject population is subjects with a clinical indication for endovascular coil and/or stent-assisted coiling embolization of cerebral aneurysms. 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.

The data collection schedule is provided in Table 1 below.

Table 1. Data collection schedule

	Pre-procedure	Procedure	Post Procedure (24 hours post-procedure or hospital discharge)
Patient Eligibility Criteria	X		
Medical History	X[1]		
Head CT angiography or MRI angiography	X[1]		
Clinical assessment & Physical exam: including: • Hunt and Hess scale • Modified Rankin score • Raymond Grade for previously coiled aneurysms • National Institutes of Health Stroke Scale (NIHSS) scale • World Federation of Neurological Surgeons (WFNS) Subarachnoid Hemorrhage (SAH) Grade • Fisher grade	X[1]		X
Raymond Grade-Roy Occlusion Classification Scale	X[3]		X
Laboratory Tests: complete blood count, hemoglobin, platelet count, platelet function testing, pregnancy test, serum creatinine and glomerular filtration rate.	X[1,2,4]		X[2]
Procedure Parameters (CorPath GRX use, procedure time, fluoroscopy time, patient radiation exposure, etc.)		X	
Angiography		X[5]	
Contrast volume		X	
Record of AEs		X	X
Data for aneurysm assessment		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.

3 Sample Size

3.1 Determination of Historical Control

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 Aneurysms (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)**
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					

	N Aneurysms (Pts)	Mortality at Discharge	Overall Complication Rate	Rupture/ perforation Rate (%)	Embolism Rate (%)
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 endobridge 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 discharge	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 Complication 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 complication	Neuro-deterioration	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 discharge	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		

3.2 Sample Size Calculation

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.

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:

H_0: $p \geq 15\%$ (5% + 10% NI margin)

H_a: $p < 15\%$,

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 safety hypothesis is:

H_0: $p \leq 80\%$ (90% - 10% NI margin)

H_a: 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.

4 Statistical Analyses and Study Objectives

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 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.

4.1 Definition of Analysis Populations

Analysis Cohort: Any subject with an attempted endovascular procedure (a non-missing robotic microcatheter insertion time).

Per-Protocol Cohort: Any subject in the analysis cohort who did not have a major protocol deviation.

4.2 Primary Effectiveness Endpoint

Objective: To assess effectiveness of using CorPath GRX for robotic-assisted endovascular procedure.

Hypothesis:

H_0: p ≤ 80% (90% - 10% NI margin)

H_a: p > 80%,

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

Endpoint: The proportion of subjects with 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.

Subjects to Include: Analysis Cohort

Statistical Analysis: The proportion of subjects with a successful procedure completion as defined will be summarized along with a 2-sided Clopper Pearson Exact 95% confidence interval. If the lower bound is greater than 80%, we will declare success and conclude that effectiveness is not inferior to the performance goal of 80%.

4.3 Primary Safety Endpoint

Objective: To assess safety of using CorPath GRX for robotic-assisted endovascular procedure.

Hypothesis:

H_0: p ≥ 15% (5% + 10% NI margin)

H_a: p < 15%,

where p=proportion of patients with a safety event.

Endpoint: The proportion of subjects with a safety event where a safety event is intra- and peri-procedural events, including target aneurysmal rupture, vessel perforation or dissection, and thromboembolic event with neurological decline within 24 hours post-procedure or hospital discharge, whichever occurs first.

Subjects to Include: Analysis Cohort

Statistical Analysis: The proportion of subjects with a safety event as defined will be summarized along with a 2-sided Clopper Pearson Exact 95% confidence interval. If the upper bound is less than 15%, we will declare success and conclude that safety is not worse than the performance goal of 15%.

4.4 Secondary Endpoints

4.4.1 Secondary Endpoint 1: Clinical Outcome

Endpoint: Defined as the clinical outcome using the Modified Rankin Scale and/or occurrence of thromboembolic events and neurological deterioration assessed by HIHSS score change (NIHSS score change > 3). This endpoint is assessed at 90 and 180 day follow-up.

Subjects to Include: Analysis Cohort

Statistical Analysis: The count and proportion of subjects with each value of the Modified Rankin Scale will be calculated along with a 2-sided Clopper Pearson Exact 95% confidence interval. The count and proportion of subjects who experience a thromboembolic event AND neurological deterioration (NIHSS score change > 3) will be calculated along with a 2-sided Clopper Pearson Exact 95% confidence interval. CRF 5 Endovascular Procedure Patient Assessment has the baseline NIHSS score, while CRF 14 90-Day Follow-Up has the 90-day mRS, and CRF 15 180-Day Follow-Up has the 180-day mRS and NIHSS score).

4.4.2 Secondary Endpoint 2: Robotically Navigate Device to the Target Aneurysm

Endpoint: Defined as successful advancement of device TO the target aneurysm robotically. Specifically, success if defined as all guidewires, microcatheters, coils, and stents that may have been used must all have been able to navigate TO the target aneurysm as identified on CRF 9 CorPath GRX Intervention Assessment CRF. Likewise, failure is any single instance where one or more of those listed items were unable to navigate to target lesion.

Subjects to Include: Analysis Cohort

Statistical Analysis: The count and proportion of aneurysms where CorPath was able to navigate TO the target lesion successfully will calculated along with a 2-sided Clopper Pearson Exact 95% confidence interval.

4.4.3 Secondary Endpoint 3: Robotically Navigate Device into the Target Aneurysm

Endpoint: Defined as successful advancement of device INTO the target aneurysm robotically. Specifically, success if defined as all guidewires, microcatheters, coils, and stents that may have been used must all have been able to navigate INTO the target aneurysm as identified on CRF 9 CorPath GRX Intervention Assessment CRF. Likewise, failure is any single instance where one or more of those listed items were unable to navigate into target lesion.

Subjects to Include: Analysis Cohort

Statistical Analysis: The count and proportion of aneurysms where CorPath was able to navigate INTO the target lesion successfully will calculated along with a 2-sided Clopper Pearson Exact 95% confidence interval.

4.4.4 Secondary Endpoint 4: Robotically Deploy Therapeutic Device into the Target Aneurysm

Endpoint: Defined as successful DEPLOYMENT of device into the target aneurysm robotically. Specifically, success if defined as all guidewires, microcatheters, coils, and stents that may have been used must all have been able to DEPLOY into the target aneurysm as identified on CRF 9 CorPath GRX Intervention Assessment CRF. Likewise, failure is any single instance where one or more of those listed items were unable to navigate into target lesion.

Subjects to Include: Analysis Cohort

Statistical Analysis: The count and proportion of aneurysms where CorPath was able to DEPLOY into the target lesion successfully will calculated along with a 2-sided Clopper Pearson Exact 95% confidence interval.

4.4.5 Secondary Endpoint 5: Overall Procedure Time

Endpoint: Defined as the time measured from the insertion of the access sheath/catheter until the removal of the microcatheter as recorded on the CRF 6 Procedure Data Form CRF.

Subjects to Include: Analysis Cohort

Statistical Analysis: The mean, standard deviation, median, interquartile range, and range along with a 2-sided 95% confidence interval for the mean will be calculated.

4.4.6 Secondary Endpoint 6: Robotic Procedure Time

Endpoint: Defined as the time measured from the first device used robotically until the removal of the microcatheter as recorded on the CRF 6 Procedure Data Form CRF.

Subjects to Include: Analysis Cohort

Statistical Analysis: The mean, standard deviation, median, interquartile range, and range along with a 2-sided 95% confidence interval for the mean will be calculated.

4.4.7 Secondary Endpoint 7: Fluoroscopy Time

Endpoint: Defined as the total fluoroscopy time during the procedure as recorded by the Imaging System on the CRF 6 Procedure Data Form CRF.

Subjects to Include: Analysis Cohort

Statistical Analysis: The mean, standard deviation, median, interquartile range, and range along with a 2-sided 95% confidence interval for the mean will be calculated.

4.4.8 Secondary Endpoint 8: Patient Radiation Exposure

Endpoint: Dose Area product (DA, mGy*cm2) and Air Kerma (AK, mGy) as recorded on the CRF 6 Procedure Data Form CRF.

Subjects to Include: Analysis Cohort

Statistical Analysis: The mean, standard deviation, median, interquartile range, and range along with a 2-sided 95% confidence interval for the mean will be calculated.

4.4.9 Secondary Endpoint 9 Contrast Fluid Volume

Endpoint: Total volume of contrast used during the procedure as recorded on the CRF 6 Procedure Data Form CRF.

Subjects to Include: Analysis Cohort

Statistical Analysis: The mean, standard deviation, median, interquartile range, and range along with a 2-sided 95% confidence interval for the mean will be calculated.

4.4.10 Secondary Endpoint 10: Adverse Events

Endpoint: All adverse events (AEs) from the start of the CorPath GRX procedure until the end of the study as recorded on CRF 11 Adverse Event / Serious Adverse Event CRF.

Subjects to Include: Analysis Cohort

Statistical Analysis: The count and percentage of subjects experiencing AEs will be summarized by Adverse Event Term and include breakdowns by seriousness and relatedness to device and procedure.

4.4.11 Secondary Endpoint 11: Thromboembolic Events

Endpoint: Defined as thromboembolic events occurring up to 180-days following the robotic-assisted procedure.

Subjects to Include: Analysis Cohort

Statistical Analysis: The count and proportion of subjects with a thromboembolic event through 180-days following the robotic-assisted procedure will calculated along with a 2-sided Clopper Pearson Exact 95% confidence interval.

4.4.12 Secondary Endpoint 12: Devices Used Robotically

Endpoints: All devices used will be recorded as successful or unsuccessful in conjunction with the CorPath GRX System. Each device used (e.g., guidewire, microcatheter, coil, etc.) is documented on CRF 9 CorPath GRX Assessment form, and an individual component needs to have successfully navigated to the aneurysm, into the aneurysm, and deployed (if applicable) into the aneurysm to be considered successful.

Subjects to Include: Analysis Cohort

Statistical Analysis: The frequency and proportion of devices successfully used that were used with a CorPath GRX System will be summarized along with a 2-sided Clopper Pearson Exact 95% confidence interval.

4.4.13 Secondary Endpoint 13: Aneurysm Occlusion

Endpoints: 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 endpoint is assessed post-procedure and at 180-day follow-up.

Subjects to Include: Analysis Cohort

Statistical Analysis: The frequency and proportion of each summary (aneurysm grade, parent-vessel compromise, occlusion durability) along with a 2-sided Clopper Pearson Exact 95% confidence interval will be summarized. Note the confidence interval for summaries of categories with more than 2 categories will be binomial confidence interval for each individual category compared to the rest.

4.5 Additional Summaries

Some additional summaries will be prepared:

- Descriptive statistics of the population
    - Demographics and patient baseline characteristics

  - Aneurysm characteristics
  - Procedures performed
- Malfunctions
- Protocol deviations

5 Data Conventions and Missing Data

It is assumed that because the primary and most secondary analyses are evaluated within twenty-four (24) hours of CorPath GRX procedure or prior to hospital discharge, whichever occurs first, there will be no 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.

6 Appendix 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 investigational medical device.

A Serious Adverse Event (SAE), as per the European Standard ISO 14155 (E), is an AE that:

- Led to death
- Led to a serious deterioration in the health of a patient that:
- Resulted in a life-threatening illness or injury
- Resulted in a permanent impairment of a body function or body structure
- Required in-patient hospitalization or prolonged hospitalization
- Resulted in medical or surgical intervention to prevent permanent impairment to a body function or body structure
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

In the current study indication, a SAE can be defined as an adverse event where the outcome is one of the following:

- 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

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.

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 is not associated with the CorPath GRX System use and is not specific to the device used. Instead, other products, surgical techniques, or medications required

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.