Medtronic

Prospective, Multi-Center, Single-Arm Study of the Reverse Medical Barrel® Vascular Reconstruction Device (VRD) for Adjunctive Treatment to Embolic Coils for Wide-Neck, Intracranial, Bifurcating/ Branching Aneurysms of Middle Cerebral and Basilar Arteries

"The BARREL Study"

Clinical Protocol
Protocol number: VRD-001
IDE Number: G130185
Revision C: May 18th, 2016

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Table of Contents

Table of Tables

Table of Figures

1. Investigator Signature Page

I agree to conduct the study as outlined in the Investigational Plan and in accordance with all applicable laws and 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 patients into this study.

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 study. It is recognized that this information may be relayed in confidence to the Institutional Review Board.

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

Investigator Signature

Date

Investigator Printed Name

2. Study Contact Personnel

3. Study Synopsis

Prospective Multi-Center Single-Arm Study of the Reverse Medical Barrel® VRD for Adjunctive Treatment to Embolic Coils for Wide-neck, Intracranial, Bifurcating/Branching Aneurysms of Middle Cerebral and Basilar Arteries: "The BARREL Study"

Title:	**The BARREL Study**
Study Device:	Reverse Medical Barrel® Vascular Reconstruction Device ("Barrel VRD")
Purpose:	To evaluate the safety and effectiveness of the Reverse Medical Barrel® VRD for Adjunctive Treatment to Embolic Coils for Wide-neck, Intracranial, Bifurcating/Branching Aneurysms of Middle Cerebral and Basilar Arteries.
Intended Use:	For use with embolic coils for the treatment of wide-neck bifurcating or branching intracranial MCA and basilar aneurysms arising from a parent vessel with a diameter of ≥ 2mm and ≤ 4 mm. "Wide-neck" is defined as having a neck width ≥ 4mm or a dome-to-neck ratio < 2.
Study Design:	The BARREL Study is a prospective multi-center, single-arm study of the Barrel® VRD. A maximum of 159 patients will be enrolled (consented) at up to 28 centers to ensure 119 treated patients. After obtaining informed consent, screening and baseline assessments, and eligibility confirmation, qualifying patients will receive the study treatment.
Inclusion Criteria:	• Male or female between 18 and 85 years old. • A wide-neck aneurysm with a neck ≥ 4mm or a dome-to-neck ratio < 2, that is also a bifurcating or branch MCA or basilar aneurysm and de novo or non-de novo MCA or basilar aneurysm where no stent was utilized. • Subject's aneurysm arises from a parent vessel with a diameter ≥ 2mm and ≤ 4mm. • Appropriate informed consent obtainable as determined by local IRB. • Life expectancy > 24 months.
Exclusion Criteria:	• Aneurysm rupture within 30 days of enrollment. • MCA or basilar bifurcating aneurysms not treatable with coiling. • Subject with anatomy not accessible for Barrel VRD treatment. • Aneurysm neck > 8 mm. • Subject presents with an intracranial mass or is currently undergoing radiation therapy for carcinoma of the head or neck region. • Subject has additional aneurysms for which treatment is planned within 18 months. • Subject has platelet count of <70,000. • Subject has had a previous intracranial stenting procedure associated with the target aneurysm. • Subject has an International Normalized Ratio (INR) ≥ 1.7 or is on one of the following anti-coagulant/anti-platelet medications : Aggrenox, Cilostazol, Apixaban, Dabigatran, Fondaparinux, Lepirudin, Pradaxa, Rivaroxaban, Argatroban, Arixtra • Subject has serum creatinine level > 2mg/dl at baseline screening. • Subject has known allergies to nickel-titanium metal. • Subject has known allergies to aspirin or heparin. • Subject has a life-threatening allergy to contrast (unless treatment for allergy can be tolerated). • Subject has a known cardiac disorder, likely to be associated with cardioembolic symptoms such as atrial fibrillation (AFIB).

	• Subject has any condition, which in the opinion of the treating physician, would place the subject at a high risk of embolic stroke. • Subject is currently participating in another clinical research study. • Subject is pregnant or breastfeeding. • Subject has participated in a drug study within the last 30 days. • Subject cannot or is unwilling to take ASA and a $P2Y_{12}$ Platelet Inhibitor as required by the protocol following the procedure. • Subject is unable or unwilling to comply with protocol requirements and obtain required clinical evaluations and follow-up.
Evaluation Criteria:	Primary Endpoints • Primary Efficacy Endpoint: The number of Barrel® VRD treated aneurysms achieving Raymond Grade I (100% occlusion) at 12 months ± 8 weeks in the absence of retreatment, parent artery stenosis (> 50%), or target aneurysm rupture. • Primary Safety Endpoint: Incidence of neurological death or major ipsilateral stroke (National Institutes of Health Stroke Scale [NIHSS] increase of ≥ 4 for >24 hours) at any time during the follow-up period (12 months ± 8 weeks).
	Secondary Endpoints • Any cause death within 30 days or neurological death within 12 months ± 8 weeks. • Number of Barrel® VRD treated aneurysms achieving Raymond Grade I or II at 12 months ± 8 weeks in the absence of retreatment, parent artery stenosis (> 50%), or target aneurysm rupture. • Number and percentage of successful device implants. • Angiographic evidence of in-stent stenosis at 12 months ± 8 weeks reported according to the following ordinal groups: <25%, 25-50%, 51-75%, >75%. • Device-related Serious Adverse Events (SAEs). • The composite percentage of patients with modified Rankin Score of 0-2 or no change from baseline at 12 months ± 8 weeks.
Schedule of Tests:	The tests and evaluations to be conducted at baseline, procedurally, and during follow-up are summarized in Table 3-1.
Statistical Considerations:	The rate of the primary efficacy endpoint will be formally compared against a historical control. The study will be conducted at up to 28 centers, and it will enroll up to 159 subjects to ensure 119 subjects are treated/undergo attempted treatment. The statistical analysis plan is detailed in Section 6.

Table 3-1 Schedule of Tests

Tests and Evaluations	Screening/ Baseline	Procedural (Day 0)	30 days ±14 days	180 days ±30 days	12 months ±8 weeks	Unscheduled Visit
Inclusion/Exclusion	X					
Demographics	X					
Medical history	X					
Medications	X	X	X	X	X	X
Blood Labs	X					
Modified Rankin Score	X		X	X	X	
NIHSS Score	X			X	X	X[5]
Adverse Events		X	X	X	X	X
Angiography[1]	X[2]	X		X[4]	X	
Raymond Grade Scale	X[3]	X		X	X	

[1]MRA is acceptable if performed according to the standard of practice at the participating institution.
[2]The baseline angiogram must be taken no more than 180 calendar days prior to the procedure.
[3]For previously coiled aneurysms
[4]If an angiogram is performed as standard patient care it should be sent to the core laboratory for analysis.
[5]If visit is related to target aneurysm or potentially associated adverse event

4. Revision History

The below table lists the protocol revision history for the BARREL study:

Table 4-1 Protocol Revision History

Revision	Effective Date
A	March 10, 2014
B	February 20th, 2015
C	May 18th, 2016

4.1 Summary of Changes

Revision A to Revision B		
Section	**Change**	**Rationale**
Sponsor	Sponsor name and study contacts changed from Reverse Medical to Covidien Neurovascular	Covidien acquired Reverse Medical and is executing the study
Study Design	Increased the number of participating centers from 20 to 28	Updated to facilitate enrollment
Exclusion criteria	Added exclusion criteria for subject with anatomy not appropriate for Barrel VRD treatment	To ensure enrollment of appropriate candidates
Exclusion criteria	Minor revision the INR and known anti-coagulant/antiplatelet agents requirement	Administrative change for clarity
Exclusion criteria Post-placement Antiplatelet Agents	Specified antiplatelet regimen dose and duration	To standardize dual antiplatelet therapy in the study
Secondary Endpoints	Change from number/percentage of "device deployments" to "device implants"	For accuracy in reporting device success
Secondary Endpoints	Change from the percentage of patients with mRS of 0-2 to also include patients with no change from baseline	Patients with no worsening from baseline should also be included in an analysis of good outcomes
Schedule of Tests Study Evaluations	Added 180 day visit, widened 30 day visit window from ±7 days to ±14 days and allowed 30 day visit to be conducted via phone, added unscheduled visit and screening blood labs; added guidance for the medications to be collected	To increase patient oversight and provide more specific instructions for unscheduled visits and medication collection
Enrollment	Updated definition to specify that enrollment occurs at the point of consent	For clarity
Statistical Analysis Sets	Intention-to-treat (ITT) population definition changed from those treated with Barrel VRD to those who underwent attempted deployment of the Barrel VRD	To include all subjects with an attempt to be treated into the ITT population
Analysis of Primary Safety Endpoint	Safety threshold lowered from 20 to 15%	Change made per recommendation noted in FDA letter dated 11 Jun 2014; rates based on incidence in published literature
Procedure	Added instructions from Instructions for Use to address coiling: refined data to be recorded during the procedure	Administrative change for clarity and to ensure that all important procedural data are captured by the investigator and/or Core Lab
Termination of Subject	Added section describing potential reasons and	Administrative change for clarity

Revision A to Revision B		
Participation	process for termination of subject participation	
Core Lab	Clarified evaluations to be performed by the Core Lab. Added instructions for assessments of 6 month and unscheduled images as applicable. Removed requirement to use blinded third party	Administrative change for clarification and for consistency with standard process at Covidien
Adverse Events	Added ISO14155 definitions for adverse events. Updated severity definitions, updated relatedness categories, as well as device specific event and event reporting requirements	To clarify collection of adverse events and for standardization with Covidien processes
Adverse Events Risk Analysis	Moved anticipated AEs to the risk analysis section in the protocol and revised the list to align with the IFU	To align risks with IFU
Responsibilities	Rewrote the following sections to align with Covidien practices: CRFs, Document Retention, DSMB, CEC, Monitoring and Publications. Added the following sections: Ethical Conduct of Study, Institutional Review Boards, Quality Control and Quality Assurance	Administrative change for standardization with Covidien processes
Appendices Informed Consent Protection of Human Subjects	Removed appendices (instructions for use and sample consent form) from protocol	Administrative change; these documents are controlled outside of the protocol

Revision B to Revision C		
Section	**Change**	**Rationale**
Sponsor	Sponsor name changed from Covidien Neurovascular to Medtronic Neurovascular	Medtronic acquired Covidien and is executing the study
Inclusion / Exclusion Criteria	Removed Prasugrel, Ticagrelor, and Ticlid from the disallowed concomitant medications list	To allow for physician standard of care prior to the procedure and align with protocol requirements of any $P2Y_{12}$ inhibitor post procedure
Inclusion / Exclusion Criteria	Removed the requirement of non-allergy to clopidrogrel and ticlopidine.	Clopidogrel is no longer a protocol required medication.
Inclusion / Exclusion Criteria	Changed the requirement from “subject cannot or is unwilling to take ASA/Clopidrogrel” to “Subject cannot or is unwilling to take ASA and a P2Y12 Platelet Inhibitor”	To align with revised dual anti-platelet therapy requirements
Primary Endpoints	Changed primary endpoint language from “absence of neurological death/major ipsilateral stroke…” to “incidence of neurological death/major ipsilateral stroke”.	Corrected the primary endpoint language for alignment with the primary safety endpoint a priori threshold of 15%
Secondary Endpoints	Changed secondary endpoint language from “absence of any cause death within 30 days…” to “Any cause death within 30 days…”	To remain consistent with primary endpoint format
Secondary Endpoints	Added language to secondary endpoint indicating stenosis will be evaluated at 12 months ± 8 weeks	Added for completeness as the timing of this endpoint had not been explicitly specified.
Secondary Endpoints	Changed secondary endpoint language from “absence of device-related serious adverse events…” to “device related serious adverse events…”	To remain consistent with primary endpoint format

Revision B to Revision C		
Section	**Change**	**Rationale**
Sample Size Calculation	• The primary performance goal was increased from 23% to 28%. • The estimated success rate of the trial was increased from 33% to 41%, therefore decreasing the necessary sample size to achieve 80% power for the trial. • Maintaining the assumption of a 10% dropout rate, the number of subjects required for the study changed from 164 to 119. • The maximum number of enrolled/consented subjects was specified as 159 to allow for screen fails.	• In conjunction with increasing the performance goal, the estimated success rate of the trial was also increased and the corresponding sample size recalculated. Based on higher estimated success rate, sample size is being reduced. • The maximum number of subjects enrolled/consented was specified to account for up to 25% of subjects who consent for the trial and may withdraw prior to treatment or are determined to be ineligible.
Statistical Analysis Sets	Removed: Note that in the case of missing primary efficacy endpoint data, the subject will be considered a failure in the primary efficacy endpoint analysis. Added: The primary analyses for both the safety and effectiveness endpoints will be based on the observed data.	Considering missing data as failure, known as the imputing worst case scenario, is an extreme imputation form and is not appropriate for the primary statistical analysis. Instead, we plan to perform primary statistical analysis based on observed cases.
Handling of Missing Data	Replaced tipping analysis for missing data with Multiple imputation technique and explanation of handling subjects who withdraw prior to the final assessment will be handled using the Markov Chain Monte Carlo algorithm to specify missing at random.	As recommended by FDA, we will apply multiple imputation technique to handle missing primary endpoints.
Post-Placement Anti-platelet Agents	Changed the dual anti-platelet therapy requirement from a minimum of 325mg of Aspirin for 12 months and 75mg of Clopidogrel daily for 3 months to the minimum of 81 mg of Aspirin for 12 months and any $P2Y_{12}$ platelet inhibitor for 3 months.	The standard of care for dual antiplatelet therapy varies across US institutions. This protocol has been updated to provide additional flexibility to investigators such that they may utilize antiplatelet regimens that are closer to their standard of care while also maintaining standardization of minimum antiplatelet requirements (minimum of two antiplatelet agents, minimum dosage and minimum duration) to prevent a wide variation in antiplatelet regimens in the study.
Follow-up Visits	Added descriptions to the 30-day and 180-day follow up visits	Administrative update to provide a clearer presentation of visit requirements. There have been no changes to the visits or assessments required.

Revision B to Revision C		
Section	**Change**	**Rationale**
Study Exit Subject Discontinuation by Investigator	Included statement regarding the requirement for follow-up through the 30-day visit for subjects who are enrolled and undergo an attempt delivery with the Barrel VRD but are not implanted This existing statement was clarified in the 'subject discontinuation by investigator' section	This requirement was added to the study exit section and revised in the 'subject discontinuation by investigator' section for clarity. The purpose for this requirement is to ensure adequate safety follow-up for subjects who do not receive the Barrel implant.
Adverse Events	Updated relatedness definitions and added definitions for select neurological adverse events of interest	To clarify collection of adverse events and for standardization with Medtronic processes
DSMB Committee	Reference to DSMB stopping rules and interim analyses have been removed	Administrative change to reflect current DSMB Charter and no plan for an interim analysis.
Clinical Events Committee	Updated types of events to be reviewed to include: 1) all Adverse Events associated with a change in NIHSS (vs. only those with a sudden neurological worsening or deterioration ≥ 3 points on the NIHSS) and 2) any Adverse Event related to the Antiplatelet Therapy	Expanded scope of adverse events to be adjudicated by the independent Clinical Events Committee for increased oversight
Multiple	Corrected spelling, grammatical, and formatting errors throughout the document	Administrative change for clarity

5. Background for Proposed Trial

In recent years, the treatment of intracranial aneurysms has shifted from a primarily surgical paradigm to one of endovascular management. The International Subarachnoid Aneurysm Trial (ISAT), published in 2002, demonstrated improved mortality and dependency rates at one year in those undergoing endovascular coil embolization to those undergoing clipping.[1] However, anatomic challenges and technological limitations continue to limit the application of endovascular techniques for many aneurysms.

In particular, wide-neck aneurysms have long been a challenge for endovascular techniques. As a result vascular remodeling (e.g., balloon or stent-assisted) embolic coiling has become increasingly common. Additionally, recent success has also been encountered with the use of flow diversion technologies.[2-4] However, limitations continue to exist, especially in branching locations for wide-neck aneurysms, which typically occur in the middle cerebral artery and basilar artery. Flow diversion is not currently approved for these locations. Recent published reports indicate that when flow diversion is used off-label in such locations, the results are dismal.[5] Therefore, the Barrel® VRD was developed specifically to address these challenging locations. Designed with an expanding central portion of the device, the Barrel® VRD is intended to protect both parent vessels for bifurcating and branching aneurysms.

The lack of technologies specifically designed to address these aneurysm subtypes is reflected in lower successful embolization rates reported in the literature. There is a paucity of literature available that specifically evaluates only branching/bifurcating aneurysms. However, in those studies that do provide evaluation, it is evident that this aneurysm subtype presents a substantially more challenging lesion with lower than typical success rates.

In an early publication, Bavinski, et al. evaluated their experience in treating 45 basilar tip aneurysms over a six year period.[9] They reported that in wide-necked basilar aneurysms complete occlusion was achieved only 15% of the time. This result was comparable to a number of other contemporaneous series. For instance, McDougall, et al. reported a 21% compete occlusion rate on follow up angiography for 19 basilar tip aneurysms and Raymond, et al. demonstrated a 19% complete occlusion rate for wide-neck basilar tip aneurysms, versus 67% complete occlusion in small neck basilar tip aneurysms.[10,11] While these early studies pre-date many modern adjunctive technologies, they

clearly illustrate the challenges associated with wide-neck branching pathologies.

More recent data demonstrates progress, but there are continued limitations when dealing with branching wide-neck aneurysms. A recent study by Lodi, et al. evaluating stent-assisted coiling in 87 aneurysms, of which 50 were located at branching (as opposed to side wall) locations, demonstrated a 31% complete occlusion rate.[12] This study used modern stent-assisted technology in all cases and included a large number of ICA sidewall locations, that are known to experience better rates of occlusion, and yet still achieved a very low rate of complete occlusion, likely secondary to the inclusion of branching wide-neck aneurysms. It should also be noted that these results, as well as all the currently published series regarding this aneurysm subtype, are self reported and not adjudicated by a core lab. A fact that is well documented to result in higher occlusion rates than core lab adjudicated series.[13,14]

There are three very recent studies that specifically address bifurcating wide-neck basilar or MCA aneurysms.[15-17] [10,11,12] Unfortunately, all of these studies are retrospective and present self-reported outcomes. The literature has repeatedly demonstrated that retrospective non-adjudicated studies consistently over-estimate treatment benefit and underestimate complications, however, these are the best data available. These data strongly demonstrate the continued limitations of current technology. Fargen, et al. reported their results treating 45 wide-neck bifurcating aneurysms with the Y-stenting technique. Despite experiencing an initial procedural/peri-procedural complication rate of 22.2%, they achieved an initial self-reported complete occlusion rate of 43%. Unfortunately, they only obtained follow-up imaging in 30 of their patients, preventing a reasonable assessment of their follow-up occlusion rates. Despite there being a high likelihood of selection bias towards the successfully treated aneurysms in the patients with follow-up, they demonstrated a self-reported 56% complete occlusion rate on follow up (when counting the two deaths as failures).[15] Overall, for their entire cohort they demonstrated successful complete occlusion on last known angiogram in 40% of patients. Spiotta, et al. likewise reported their retrospective non-adjudicated results treating 19 patients with bifurcating aneurysms with stent-assisted coiling.[16] They experienced a 32% complication rate and achieved an initial self-reported complete occlusion rate of 26%. On follow-up imaging they self-reported a 53% complete occlusion rate (without re-treatment), and for their entire cohort they demonstrated 47% of patients having complete occlusion on last known angiogram. The final series evaluating stent-assisted embolization of wide-neck bifurcating basilar aneurysms is a very recent publication by Zhang, et al.[17] They report their results with treating 23 wide-necked basilar aneurysms. In this study, the authors report a self-adjudicated complete occlusion rate of 39.1%. Mean angiographic follow-up at 13.5 months was reported for 16 patients. Within that selected cohort they experienced a self-reported complete occlusion rate of 62%, with a self-reported all patients' complete occlusion rate of 43%.[17]

Despite substantial progress over the past decade, endovascular treatment of bifurcating aneurysms remains a significant challenge. Despite the lack of independent adjudication, a composite analysis (all complete occlusions divided by the total number of patients), of the above reviewed modern studies demonstrate only a 42% overall complete occlusion rate at follow-up. The mean and standard deviation of all three studies (treating each study as a single entity) is 43% and 3.5%, respectively. Again, it is worth noting that all of these studies were retrospective and un-adjudicated, significant contrasts to the proposed prospective adjudicated study, and a methodology well demonstrated to overestimate successful occlusion rates and underestimate complication rates. However, these data are the best available for this disease state.

6. Statistical Considerations and Analysis

The primary efficacy endpoint to be evaluated in this study is the outcome of treated aneurysms from study subjects achieving Raymond[18] Grade I (100% occlusion) at 12 months ± 8 weeks in the absence of retreatment, parent artery stenosis (> 50%), or target aneurysm rupture. The rate of the primary efficacy endpoint will be formally compared to a historical control, which is derived using a meta-analysis of the three very recent studies that specifically address bifurcating wide-neck basilar or MCA aneurysms (Fargen et al, 2013[15]; Spiotta et al, 2011[16]; and Zhang et al, 2014[17]) as summarized in the Table 6-1. The study will be conducted at up to 28 centers and will enroll up to 159 subjects to ensure treatment/attempted treatment of 119 subjects (107 evaluable assuming a 10% loss to follow-up rate).

6.1 Determination of Historical Control

The BARREL Study is designed as a single-arm trial, which will be compared against a historical control derived from a meta-analysis of the rate of primary efficacy endpoint. i.e. outcome of treated aneurysms from study subjects achieving Raymond Grade I (100% occlusion) at 12 months ± 8 weeks in the absence of retreatment, parent artery stenosis (> 50%), or target aneurysm rupture. A follow-up target of 12 months was chosen specifically because it matches the mean follow-up of the meta-analysis.[18] The Table 6-1 summarizes types of aneurysms, demographic information, and clinical outcomes of three very recent studies that specifically address wide-necked basilar and MCA aneurysms. Information about these studies is summarized in Section 5, "Background for Proposed Trial". An overall estimate of the rate of the primary efficacy endpoint derived from the meta-analysis of these three trials is 42.5% with the 95% confidence interval of (31.90%, 53.06%). This overall estimate provides the basis for deriving the historical control.

Table 6-1 Meta-Analysis for Historical Control

Study	Number of Aneurysms in the Trial	Number of Bifurcation Aneurysms in the Trial	Number of Wide-Necked Aneurysms in the Trial	Mean Age	Number of Women	Follow-up Time (Months)	Number with Angiographic Follow-up	Number of Raymond Grade I at Follow-up	% of Raymond Grade I of those Followed-up	% of Raymond Grade I of Cohort
Fargen 2013	45	45 (100%)	45 (100%)	57.9	31 (69%)	9.8	30	18	56%	40% (18/45)
Spiotta 2011	19	19 (100%)	19 (100%)	57.4	14 (74%)	16	17	9	52.90%	47% (9/19)
Zhang 2014	23	23 (100%)	23 (100%)	51.2	12 (51%)	13.5	16	10	62.5%	43% (10/23)
Total	**87**	**87 (100%)**	**87 (100%)**		**57 (66%)**	**12.1**	**63**	**37**	**57.1%**	**42.5% (37/87)**

The estimation of the rate of the primary endpoint derived from the three referenced studies, using the weighted proportion and its standard error (SE), was calculated using the following formula:

$$\hat{P} = \frac{\sum_i W_i p_i}{\sum_i W_i}, \textit{ where } \hat{P} \textit{ is the combined rate of complete occlusion;}$$

p_i *is the rate of complete occlusion in each referenced study;*

$$W_i = \frac{1}{S_i^2}; S_i^2 = \frac{p_i(1-p_i)}{n_i}; \qquad \textit{where } n_i \textit{ is the sample size of each reviewed study;}$$

$$SE\left(\hat{P}\right) = \sqrt{\left(\sum W_i\right)^{-1}}$$

and the 95% confidence interval (CI) is $\hat{P}$ ± 1.96 * *SE(* $\hat{P}$ *).*

6.2 Primary Analysis

The goal of the primary analysis will be to demonstrate that the Barrel® VRD device performs better than the combined historical control treatments for complete occlusion rate at 12 months. The hypothesis to be tested is:

$$H_0: \pi_B = HC \text{ versus } H_A: \pi_B > HC$$

Where π_B is the proportion of successful outcomes for the Barrel® VRD device and HC is the combined overall historical control success rate. Success is defined as a subject with a Raymond Grade of 1 (100% occlusion) at 12 months ± 8 weeks in the absence of retreatment, parent artery stenosis (> 50%), or target aneurysm rupture. This hypothesis will be tested using an exact one sample binomial test at ($\alpha = 0.025$). Exact 95% confidence intervals will be constructed.

The meta-analysis analysis mentioned above provides an overall estimate for historical control success rate of 42.48% with a 95% confidence interval of (31.90%, 53.06%).

Although the meta-analysis provides the basis for deriving a historical control success rate, it does not allow exact comparison due to the author-evaluated Raymond Grades used in the studies versus the proposed core laboratory grade reporting. Moreover, the reported rates in the published literature do not take into account patients lost to follow-up in their final calculation of occlusion rates. Conversely, the Barrel study employs a more stringent intent-to-treat (ITT) methodology that treats those patients lost to follow up as treatment failures. A review of the literature shows that onsite angiographic evaluators report 20 to 60% higher Raymond Grade success rates than those reported by core laboratories.[13,14] Rezek et al. (2013)[14] states "Core laboratories tend to report higher rates of unfavorable outcomes compared with self–reporting centers. Indeed, the rate of unfavorable outcomes was 43.6% greater in core laboratories compared with noncore laboratory studies." McDougall CG et al. (2014)[19] states, "in 36% of cases, the local investigators reported a better degree of occlusion than did the core laboratory."

Unfortunately only one paper, Rezek et al. (2014)[13], provided sufficient detail of the operator and core laboratory

results, in a population that is representative of the patient population that is proposed in the protocol, to allow statistical analysis of the difference.

An analysis of this data provided an adjustment of 36% between the operator results and the core laboratory results. This difference was consistent with the other published results. After adjustment, the estimated historical success rate for core lab results is 28%. The corresponding adjusted confidence interval is (23%, 33%).

6.3 Sample Size Calculation

In actuality, the real objective of this study is to demonstrate that the Barrel® VRD is comparable to historical controls. Therefore the historical success rate of 28% was selected as the historical control value. The Barrel® VRD will be considered successful if its lower 95% confidence limit is greater than 28%.

Table 6-2 presents the sample size necessary to have an 80% power with a significance level of 2.5% for rejecting the null hypothesis in favor of the alternative when the true success rate for the Barrel® VRD is as specified. The hypotheses to be tested are:

$$H_0: \pi_B = 28\% \text{ versus } H_A: \pi_B > 28\%$$

Where π_B is the proportion of successful outcomes for the Barrel® VRD device.

Table 6-2 Sample Size

	True Success Rate for Barrel® VRD Device							
% Raymond Grade 1	38%	39%	40%	41%	42%	43%	44%	45%
Sample Size	177	145	123	107	92	80	71	62

Principal Investigator J Mocco, MD and the clinical team agree that there is potentially an advantage to the Barrel® VRD device and thus a 41% success rate is the expected performance. Assuming a 10% dropout rate, the number of subjects required to be treated for the study is 119. The total number of subjects enrolled will be 159 to account for up to 25% of subjects who consent for the trial and withdraw prior to treatment or are determined to be ineligible.

6.4 Endpoint Analysis and Reporting of Results

All statistical analyses will be performed using SAS Version 9.2 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 will also be provided.

6.5 Statistical Analysis Sets

The primary analysis set will be based on the intention-to-treat (ITT) population set. For this study, all subjects who meet the study entry criteria, sign the written informed consent (enrolled), and undergo attempted delivery with the Barrel VRD will be counted in the primary analysis set of ITT.

Analysis will also be performed on the per-protocol population set, defined as all subjects included in the ITT population set who have complied with the protocol without major protocol deviations, and have completed the 12-month angiographic evaluation.

The primary analyses for both the safety and effectiveness endpoints will be based on the observed data.

6.6 Analysis of Primary Safety Endpoint

The primary safety endpoint is defined as the incidence of neurological death or major ipsilateral stroke (National Institute of Health Stroke Scale [NIHSS] increase of ≥ 4 for >24 hours) at any time during the follow-up period (12 months ± 8 weeks). Total number and frequency of subjects with neurological death or major ipsilateral stroke will be presented with two-sided 95% confidence intervals of the rate.

The primary safety endpoint will be met if the upper bound of the confidence interval is ≤ 15%. Table 6-3 below summarizes the clinical outcomes of the three studies from the background that specifically address endovascular treatment of wide-necked basilar and MCA aneurysms. Information about these studies is summarized in Section 5, "Background for Proposed Trial". A complication rate was identified for each article by including events which could indicate stroke (i.e., thromboembolic events, ischemic events, artery dissection, hemorrhage, aneurysm rupture, and cranial nerve palsy). The overall weighted average of the incidence rate derived from the meta-analysis of these three trials was 13%. This provides the basis for selecting 15% for the primary safety endpoint of the Barrel study.

Table 6-3 Safety Rates Reported in the Literature

Study	Number of Patients in the Trial	Number of Aneurysms in the Trial	Number of Events	Complication* Rate
Fargen 2013	45	45	6	13.3%
Spiotta 2011	19	19	4	21.1%
Zhang 2014	23	23	1	4.3%
Total / Weighted Average	87	87	11	12.6%

* Complications include events that could indicate stoke (i.e., thromboembolic events, ischemic events, artery dissection, hemorrhage, aneurysm rupture and cranial nerve palsy)
Note: These articles were reviewed closely to ensure that if the information was available, that patients with multiple complications were counted only once, as well as to ensure that asymptomatic events and events resolving within 24 hours were excluded.

6.7 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, maximum, and 95% confidence interval of the mean.

6.8 Analysis of Baseline Demographics and Procedural Characteristics

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

6.9 Pre-planned Subgroup Analyses

Subgroup analysis of demographic factors of age group (≤ 65 and > 65) and gender (male and female) will be

performed.

6.10 Handling of Missing Data

Multiple imputation technique will be implemented to assess the impact of missing data on the analysis of efficacy endpoint. For the parameters summarized based on the incidence, an imputed dataset where the binary outcome for subjects who withdraw prior to the scheduled assessment will be derived using the Markov Chain Monte Carlo (MCMC) algorithm specifying missing at random (MAR). The subject characteristics and demographic factors to be included in the multiple imputation procedure to generate the imputed datasets for analysis will be defined in the Statistical Analysis Plan (SAP).

7. Objectives

The purpose of this study is to evaluate the safety and efficacy of the Reverse Medical Barrel® VRD for Adjunctive Treatment to Embolic Coils for Wide-neck, Intracranial, Bifurcating/Branching Aneurysms of Middle Cerebral and Basilar Arteries.

8. Overall Trial Design

The BARREL Study is a prospective multi-center single-arm study of the Barrel® VRD. Up to 159 subjects will be enrolled at up to 28 centers to ensure 119 subjects are treated. After obtaining informed consent, screening and baseline assessments, and eligibility confirmation, qualifying patients will receive the study treatment.

8.1 Primary Outcome Measures

8.1.1 Primary Endpoints

- Primary Efficacy Endpoint: The number of Barrel® VRD treated aneurysms achieving Raymond Grade I (100% occlusion) at 12 months ± 8 weeks in the absence of retreatment, parent artery stenosis (> 50%), or target aneurysm rupture.[18] The primary efficacy endpoint will be met if the lower bound of the 95% confidence interval is > 23%.
- Primary Safety Endpoint: Incidence of neurological death or major ipsilateral stroke (National Institutes of Health Stroke Scale [NIHSS] increase of ≥ 4 for >24 hours) at any time during the follow-up period (12 months ± 8 weeks). The primary safety endpoint will be met if the upper bound of the confidence interval is ≤ 15%.

8.1.2 Secondary Endpoints

- Any cause death within 30 days or neurological death within 12 months ± 8 weeks.
- Number of Barrel® VRD treated aneurysms achieving Raymond Grade I or II at 12 months ± 8 weeks in the absence of retreatment, parent artery stenosis (> 50%), or target aneurysm rupture.
- Number and percentage of successful device implants
- Angiographic evidence of in-stent stenosis at 12 months ± 8 weeks reported according to the following ordinal groups: <25%, 25-50%, 51-75%, >75%.
- Device-related Serious Adverse Events (SAEs).
- The composite percentage of patients with modified Rankin Score of 0-2 or no change from

baseline at 12 months ± 8 weeks.

9. Trial Population

9.1 Number of Patients

A maximum of 159 subjects will be enrolled (consented) into the study at up to 28 centers to ensure the study has an adequate number of treated subjects; up to 119. The duration of the study participation is 12 months ± 8 weeks and the total expected study duration, including completion of all follow-up requirements, is approximately 2.5 years.

9.2 Patient Inclusion Criteria

A subject who meets all of the following criteria may be included in the trial:

1. Male or female between 18 and 85 years old.
2. A wide-neck aneurysm with a neck ≥ 4mm or a dome-to-neck ratio < 2, that is also a bifurcating or branch MCA or basilar aneurysm and de novo or non-de novo MCA or basilar aneurysm where no stent was utilized.
3. Subject's aneurysm arises from a parent vessel with a diameter ≥ 2mm and ≤ 4mm.
4. Appropriate informed consent obtainable as determined by local IRB.
5. Life expectancy > 24 months.

9.3 Patient Exclusion Criteria

A subject who meets any of the following criteria will not be included in the trial:

1. Aneurysm rupture within 30 days of enrollment.
2. MCA or basilar bifurcating aneurysms not treatable with coiling.
3. Subject with anatomy not accessible for Barrel VRD treatment.
4. Aneurysm neck > 8 mm.
5. Subject presents with an intracranial mass or is currently undergoing radiation therapy for carcinoma of the head or neck region.
6. Subject has additional aneurysms for which treatment is planned within 18 months.
7. Subject has platelet count of <70,000.
8. Subject has had a previous intracranial stenting procedure associated with the target aneurysm.
9. Subject has an International Normalized Ratio (INR) ≥ 1.7 or is on one of the following anti-coagulant/anti-platelet medications: Aggrenox, Cilostazol, Apixaban, Dabigatran, Fondaparinux, Lepirudin, Pradaxa, Rivaroxaban, Argatroban, Arixtra.
10. Subject has serum creatinine level > 2mg/dl at baseline screening.
11. Subject has known allergies to nickel-titanium metal.
12. Subject has known allergies to aspirin or heparin.
13. Subject has a life-threatening allergy to contrast (unless treatment for allergy can be tolerated).
14. Subject has a known cardiac disorder, likely to be associated with cardioembolic symptoms such as atrial fibrillation (AFIB).
15. Subject has any condition, which in the opinion of the treating physician, would place the subject at a high risk of embolic stroke.
16. Subject is currently participating in another clinical research study.
17. Subject is pregnant or breastfeeding.

18. Subject has participated in a drug study within the last 30 days.
19. Subject cannot or is unwilling to take ASA and a $P2Y_{12}$ Platelet Inhibitor as required by the protocol following the procedure.
20. Subject is unable or unwilling to comply with protocol requirements and obtain required clinical evaluations and follow-up.

Before any subject is enrolled in the study, the baseline angiogram will be reviewed by a Barrel expert to ensure that the target intracranial aneurysm (IA) is amenable to treatment with the Barrel VRD device.

10. Device Descriptions

The Barrel® VRD features a self-expanding design that allows it to be completely deployed and fully retrieved.

The Barrel® VRD is comprised of nitinol and several platinum marker bands. The proximal marker band attaches to a wire that pushes the device through a commercially available 0.021" microcatheter to the intended treatment site. The delivery wire detaches from the Barrel® VRD by electrolytic means after deployment with the Reverse Medical® Detachment System (Model ED2-RM-VRD).

The Barrel® VRD is packaged as a single unit with the detachable delivery wire and introducer sheath. The system is provided sterile, non-pyrogenic, and is intended for single use only. The Barrel® VRD is not commercially available and is considered investigational in this study. The Barrel® VRD and components are required to be used per the protocol and as specified in the IDE Instructions for Use (IFU) document.

The Reverse Medical® Detachment System is a battery-operated device designed to initiate and control detachment of Reverse Medical® detachable implants within the vasculature. The Reverse Medical® Detachment System is designed for multiple uses, but the battery must be removed and the unit cleaned after each procedure. A new battery should always be inserted into the Detachment Box before each procedure.

The Reverse Medical® Detachment System is designed to apply a constant current and detect System detachment. It maintains a current by sensing the amount of resistance to current flow and adjusting the voltage required to maintain a constant current.

The Reverse Medical® Detachment System is designed to identify the changes in voltage required by the System associated with detachment. Once detachment is identified, the Detachment System indicates detachment with an audible and visual "Detach" signal and stops the flow of current to the System.

A Reverse Medical Cable Set – 275 cm length (Model RMCS – 2.75VRD) is provided sterile and is for single use only. The cable set connects to the Detachment Box through a bayonet type dual pin connector that ensures correct polarity. The Reverse Medical Cable Set and Detachment Box will be provided at no charge separately. One 9-volt battery and a sterile needle (20 G or 22 G) will also be needed for the embolization procedure.

The Barrel® VRD is specifically designed for use with the Reverse Medical® Detachment System and Cable Set. This Reverse Medical® Detachment System will be provided separately. The Barrel® VRD and Detachment System are depicted in Figures 10-1 through 10-4 and Table 10-1.

Figure 10-1 Detachment Zone and Delivery Wire of Barrel® VRD

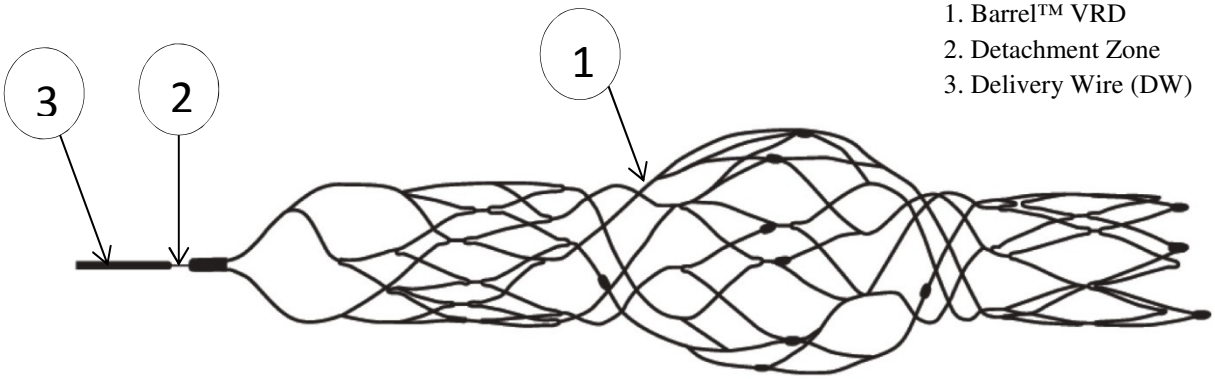

Figure 10-2 Image of Actual Barrel® VRD

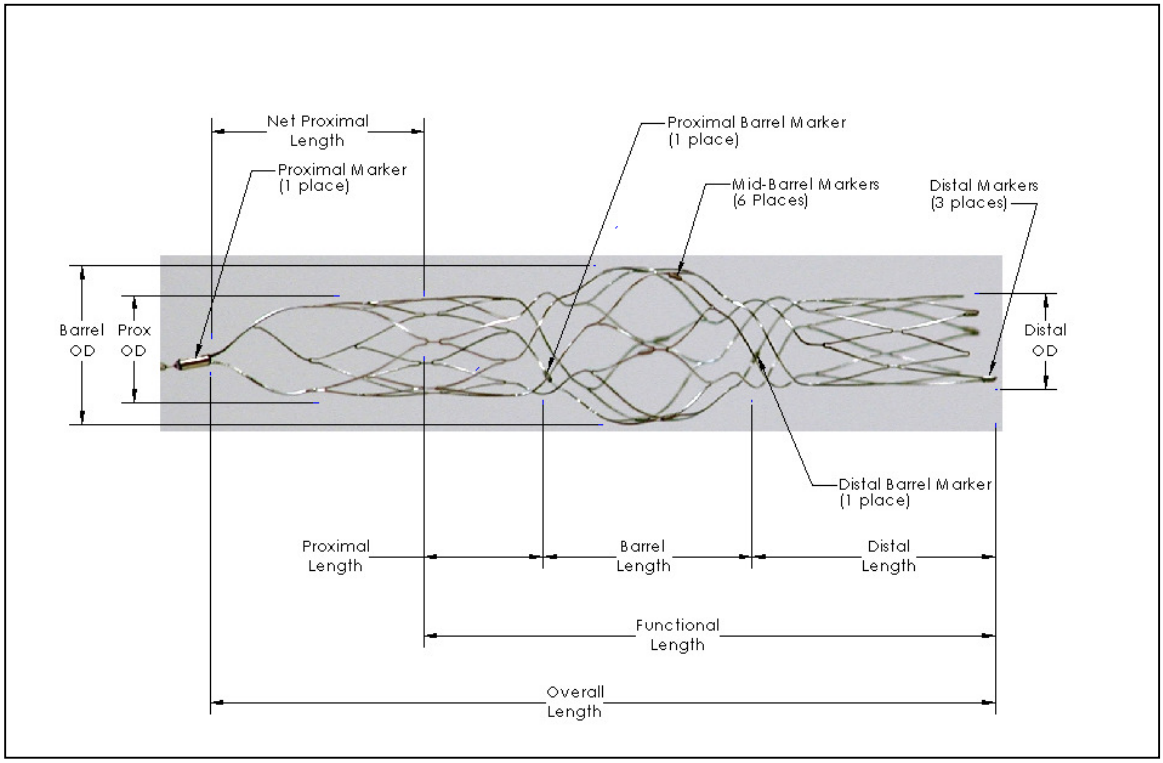

Table 10-1 Materials Used in the Barrel® VRD

Nitinol Wire (Heat treated, Laser Cut, Electropolished)
Platinum Wire
Steel, Stainless 301
Solder
Sheath, Polypropylene
Urethane Adhesive
Cyanoacrylate Adhesive
Platinum Marker band
Urethane Adhesive

Figure 10-3 Cable Set

Item	Description / Material
1	Clip - ABS plastic, copper wire
2	Cable – copper wire, silicone jacket insulation (2.75M in length)
3	Connector - ABS plastic, copper wire

Figure 10-4 Reverse Medical Detachment Box

Detachment box housing: ABS plastic

Width: 79mm
Depth (without I.V. clamp): 33mm
Depth (with I.V. clamp): 72mm
Height: 126mm

11. Study Materials

11.1 Instructions for Use

Instructions for the delivery and release of the Barrel® Vascular Reconstruction Device are outlined in the Barrel® VRD Instructions For Use (IFU) and the Reverse Medical® Detachment System IFU.

11.2 Device Accountability

Investigators will be provided with sterile investigational products including Barrel® VRDs, Cable Sets, and Detachment Boxes. Complete accountability for each device must be maintained. Any unused devices must be returned to the Sponsor at the conclusion of the study or upon product expiration.

12. Study Methods and Procedures

12.1 Enrollment Procedures

Prospective patients, as defined by the inclusion and exclusion criteria, will be considered for enrollment in this trial. Enrollment will be considered the point of consent. Prior to enrolling a patient, it must be verified that all criteria are met. Patients must meet **all** of the inclusion criteria and **none** of the exclusion criteria prior to treatment in the study.

12.2 Informed Consent

This protocol requires written informed consent, in accordance with applicable federal, state, and study center regulations. This consent shall be obtained from each patient, or appropriate surrogate, prior to the investigational procedure. The Investigator will retain a copy of the signed informed consent document in each subject's record, and provide a copy to the subject. The Investigator shall not request the written informed consent of any patient, and shall not allow any patient to participate in the study before obtaining Institutional Review Board (IRB) approval.

Prior to starting the study, the Investigator will provide Medtronic with a copy of the Informed Consent Document approved by the IRB with documented evidence that the protocol has received IRB approval.

12.3 Physician Training

Physicians who participate in this study will be trained using a phantom or bench-top model of the Barrel® VRD under fluoroscopic visualization.

12.4 Schedule of Events

The tests and evaluations to be conducted at baseline, procedurally, and during follow-up are summarized in the Table 12-1.

Table 12-1 Schedule of Tests

Tests and Evaluations	Screening/ Baseline	Procedural (Day 0)	30 days ±14 days	180 days ±30 days	12 months ±8 weeks	Unscheduled Visit
Inclusion/Exclusion	X					
Demographics	X					
Medical history	X					
Medications	X	X	X	X	X	X
Blood Labs	X					
Modified Rankin Score	X		X	X	X	
NIHSS Score	X			X	X	X[5]
Adverse Events		X	X	X	X	X
Angiography[1]	X[2]	X		X[4]	X	
Raymond Grade Scale	X[3]	X		X	X	

[1]MRA is acceptable if performed according to the standard of practice at the participating institution.
[2]The baseline angiogram must be taken no more than 180 calendar days prior to the procedure.
[3]For previously coiled aneurysms
[4]If an angiogram is performed as standard patient care it should be sent to the core laboratory for analysis.
[5]If visit is related to target aneurysm or potentially associated adverse event

12.5 Procedure

Access the targeted vessel and perform an angiogram using standard technique. Advance the Barrel® VRD through a 0.021 microcatheter to the desired position and deploy the device utilizing the delivery wire. Detach the delivery wire from the Barrel® VRD using the Reverse Medical® Detachment System and remove the microcatheter from the subject.

Use the following steps to administer coils:

a. Use a guidewire and microcatheter to access the aneurysm through the device's struts.
b. After the microcatheter has been positioned within the aneurysm, detachable embolization coils can be deposited into the aneurysm per manufacturer's instructions.
c. Warning – Observe the VRD's marker position during the coiling procedure to ensure the VRD does not migrate from detached position.
d. After placement of the last coil, verify the VRD has remained patent and properly positioned.
e. Carefully remove the microcatheter from the VRD's struts.

12.6 Study Evaluations

12.6.1 Screening/Baseline Evaluations

The following information will be collected:

- Inclusion/Exclusion Criteria
- Demographics
- Medical History
- Medications
- Modified Rankin Score
- NIHSS Score
- Angiography data
- Raymond Grade for previously coiled aneurysms

All medications that a patient is taking starting 30 days prior to screening will be collected and followed for the duration of the study. In addition, the following medications will be collected throughout the study: antithrombotic, antiplatelet, anticoagulant, inhibitor of ADP-induced platelet aggregation, all medications administered during the study procedure, and medications associated with adverse events.

12.6.2 Procedural Evaluations

During the operative procedure the following information will be recorded:

- Devices and components used (Barrel® VRD, guidewires, and delivery catheters) including manufacturer and model number
- Puncture time
- Detachment time
- Location of aneurysm
- Coiling packing density
- Device implant success (yes/no), defined as the ability to implant the device in the target area
- Stenosis in the parent artery
- Intra-operative complications
- Presence of vasospasms (time of onset, vessels involved, time resolved). Vasospasm will be recorded as an AE only if it led to a subsequent thrombotic or ischemic event.
- Medications

12.6.3 Immediate Post-operative Evaluations

The following information will be recorded during the immediate post-operative evaluation:

- Angiographic assessment
  - Stenosis
  - Raymond Grade[18]

    Class 1: Complete occlusion - complete obliteration of the aneurysm.

    Class 2: 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 3: Residual aneurysm - opacification of the aneurysmal sac.
- Description of adverse events
- Medications

12.6.4 Post-placement Antiplatelet Agents

Antiplatelet agents will be given after the Barrel device placement procedure as defined below:

- Aspirin**:** At least 81 mg daily for a minimum of 12 months
- $P2Y_{12}$ Platelet Inhibitor**:** Daily for a minimum of 3 months

Medications could be continued beyond above regimen if medically indicated.

12.6.5 Follow-Up (30-day, 180-day, and 12-month)

The following assessment will be completed at the specified time points below. All visits should be completed by study subjects with successful implant of the Barrel VRD. Subjects that underwent attempted delivery with the Barrel VRD, but were not implanted should complete the 30-day visit and be exited from the study.

- 30 Day ± 14 Days
  - Neurologic Evaluation
    - The Investigator is responsible for ensuring that the administration of the modified Rankin Score is conducted by a trained person with appropriate qualifications to perform these evaluations.
  - Details of any additional (subsequent) procedures or additional treatments
  - Description of adverse events, including the time of onset
  - Medication Usage
  - 30 day evaluations may be performed remotely via telephone if subject is not available for a visit to the study center.

- 180 Day ± 30 days
  - Neurologic Evaluation
    - The Investigator is responsible for ensuring that the administration of the NIHSS and modified Rankin Score are conducted by a trained person with appropriate qualifications to perform these evaluations.
  - Details of any additional (subsequent) procedures or additional treatments
  - Angiographic assessment (if done as standard of care)
    - Stenosis
    - Raymond grade
  - Description of adverse events, including the time of onset
  - Medication Usage
- 12 month ± 60 days
  - Neurologic Evaluation

    The Investigator is responsible for ensuring that the administration of the NIHSS and modified Rankin Score are conducted by a trained person with appropriate qualifications to perform these evaluations.
  - Details of any additional (subsequent) procedures or additional treatments
  - Angiographic assessment
    - Stenosis
    - Raymond grade
  - Description of adverse events, including the time of onset
  - Medication Usage

12.6.6 Unscheduled Visits

Any visit by the subject to the Investigator related to the target IA treated or a potentially associated adverse event should include a neurologic examination using NIHSS. The Investigator should document the review of the adverse event status and all relevant medications taken by the subject.

12.6.7 Study Exit

Upon completion of the specified study follow-up at 12 months the subject will be exempt from further data collection. The subject will be seen by the treating physician according to standard care following intracranial aneurysm treatment. If the subject underwent attempted delivery with the Barrel VRD but did not receive a Barrel VRD implant, the subject will be exited from the study following the 30 day visit.

12.6.8 Termination of Subject Participation

Subjects may withdraw from the study at any time without penalty or loss of medical care, or they may be withdrawn at any time at the discretion of the Principal Investigator (PI) or Sponsor for safety or administrative reasons.

12.6.8.1 Subject withdrawal

All enrolled subjects have the right to withdraw their consent at any time during this study. All data collected until the time of subject withdrawal will remain in the study database and will be used for analysis. Whenever possible, the site staff should obtain written documentation from the subject who wishes to withdraw his/her consent for future follow-up visits. If the site staff is unable to obtain written documentation, all information regarding the subject's withdrawal must be recorded in the subject's medical record. In addition, the appropriate eCRFs must be completed for the subject and clear documentation of the subject's withdrawal should be provided to the Sponsor.

12.6.8.2 Subject discontinuation by investigator

An Investigator may discontinue a subject from the study, with or without the subject's consent, for any reason that may, in the Investigator's opinion, negatively affect the well-being of the subject. If a subject is withdrawn from the study, the Investigator will promptly inform the subject and Sponsor. If a subject is enrolled and undergoes attempted delivery with the Barrel VRD without successful implant of the investigational device, the subject will be exited from the study following the 30 day visit.

12.6.8.3 Lost to follow-up

A subject will be considered lost to follow-up if the subject cannot be reached after three (3) attempts to contact the subject for the 1 year visit. The site must document a minimum of three (3) attempts, and the final documented attempt should be made via registered letter.

12.6.8.4 Discontinuation by IRB

The IRB/EC may choose to discontinue the study at any center(s) for which they granted approval if:

- The research study is not conducted in accordance with the IRB/EC's requirements.
- The research study indicates unexpected serious harm to subjects.

12.6.8.5 Study Discontinuation by Sponsor

The Sponsor may choose to discontinue the study should the Sponsor discover additional information during the study that may cause harm to subject safety.

If the study is terminated prematurely or suspended, the Sponsor will promptly inform all clinical Investigators of the termination or suspension and the reason(s) for this. The IRB/EC will also be informed, either by the Sponsor or Investigator if a local IRB/EC is utilized, promptly and provided with the reasons(s) for the termination. If applicable, regulatory authorities will be informed. Enrolled subjects will be asked to complete all remaining study visits and the subject will then be seen by the treating physician according to standard care following intracranial aneurysm treatment.

12.7 Angiography Core Lab

12.7.1 Assessments

The following assessments will be made by the Angiography Core Lab from images submitted from the sites. The images 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 grade (pre-procedure required only for previously coiled aneurysms)
- Stenosis of parent and branch arteries (pre-procedure)

180 days ± 30 days post-procedure

- Stenosis of parent and branch arteries
- Raymond grade
- In-stent stenosis

12 months ± 8 weeks post-procedure

- Stenosis of parent and branch arteries
- Raymond grade
- In-stent stenosis

Unscheduled

- Stenosis of parent and branch arteries
- Raymond grade
- In-stent stenosis

12.8 Adverse Event Reporting

All adverse events will be collected during the course of the study on the eCRFs.

Adverse event status will be evaluated throughout the study. These will include events occurring from the point of consent until a subject exits the study. 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 a serious and/or unexpected event requiring notification to the Sponsor, regulatory agency, and as applicable, IRB/EC, within the specified reporting timeframe. AEs will be categorized using the definitions in **Section 12.8.1**.

All study AEs, as well as the treatment and follow-up required, should be documented in the subject's medical records and in the eCRF. All study AEs will be followed by the Investigator until resolution or until the end of the 12 month follow-up. A list of potential anticipated adverse events is provided in **Section 13**.

All relevant medical conditions reported at screening/baseline visit will be recorded in the medical history form, including any signs and symptoms related to the condition of intra-cranial aneurysm.

12.8.1 Definitions

An **Adverse Event (AE)** is defined as 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. (ISO 14155:2011)
Note 1: This includes events related to the investigational device or the comparator.
Note 2: This includes events related to the procedures involved (any procedure in the clinical investigational plan).
Note 3: For users or other persons this is restricted to events related to the investigational medical device.

An **Adverse Device Effect (ADE)** is defined as an adverse event related to the use of an investigational medical device. (ISO 14155:2011) The investigational medical devices for this study are the Barrel® VRD, and the Reverse Medical® Detachment System.
Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational device.
Note 2: This includes any event that is a result of a use error or intentional misuse of the investigational medical device.

A **Serious Adverse Event (SAE)** is defined as an AE that:

a) Led to death,

b) Led to serious deterioration in the health of the subject, that either resulted in

1. A life-threatening illness or injury, or
2. A permanent impairment of a body structure or a body function, or
3. In-patient or prolonged hospitalization, or
4. Medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect (ISO 14155:2011)

Note 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

Note 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigational Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

A **Serious Adverse Device Effect (SADE)** is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011)

An **Unanticipated Serious Adverse Device Effect (USADE)** is defined as a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. (ISO 14155:2011)
Note: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

An **Unanticipated Adverse Device Effect (UADE)** is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3)

Severity:

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

Relatedness:

- Study Disease-related: Event is clearly attributable to the underlying study disease state (aneurysm) or concomitant medications taken for these with no temporal relationship to the device, procedure , or concomitant medications.
- Concomitant disease-related: Event is clearly attributable to an underlying concomitant disease state or concomitant medication taken for these with no temporal relationship to the device, procedure/treatment, or study disease state.
- Procedure-related: Event has a strong temporal relationship to the study procedure. This includes AEs attributable to any device(s) other than the Barrel® VRD, Detachment Box, or Detachment Cables used at procedure (day 0), 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 study device (the Barrel® VRD, Detachment Box, or Detachment Cables), and alternative etiology is less likely.

  All events considered "device-related" will be further characterized as either:

  - Anticipated: When the event was previously identified in nature, severity or degree of incidence in the investigational plan. Or
  - Unanticipated: When the event was not previously identified in nature, severity or degree of incidence in the investigational plan.
- Non-index procedure related: This includes AEs attributable to any device(s) used at procedures other than day 0, such as access devices, delivery microcatheters, non-ionic contrast, guidewires, or any other adjunctive, approved/cleared device for treatment of intracranial aneurysms.
- Antiplatelet therapy-related: Event is clearly attributable to antiplatelet therapy with no temporal relationship to the device, treatment, or medical history
- Unknown: Event relationship cannot be attributed to any of the above categories, and remains undetermined.

A **Stroke** is defined as 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.

The definition includes:

- Subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction.

The definition excludes:

- Slowly progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth.
- Stroke events in cases of blood disorders such as leukemia or external events such as trauma.
- Transient ischemic attacks, in which the symptoms resolve on their own within 24 hours

Stroke severity will be graded by the CEC as major or minor:

- Major Stroke: A stroke which increases the NIH Stroke Scale of the subject by ≥ 4.
- Minor Stroke: A stroke which increases the NIH Stroke Scale of the subject by ≤ 3.

The term "ipsilateral" in the primary safety endpoint definition will be defined as "on the same side of the brain as the target aneurysm" for MCA aneurysms and as "in the territory supplied by the treated artery" for basilar aneurysms.

Each stroke event will be adjudicated for "Ipsilateral" site of occurrence:

- Ipsilateral for MCA strokes
- In the territory supplied by the treated artery for Basilar artery strokes as adjudicated by the Clinical Events Committee

A **Neurological Death** is any subject death due to neurological reasons.

An **Intra-Cranial Hemorrhage (ICH)** is a hemorrhage within the fixed vault of the cranium (skull). These will be further categorized as:

- **Intra Cerebral Hemorrhage:**
    - Intra Ventricular Hemorrhage (IVH): Hemorrhage within the ventricles
    - Intra Parenchymal Hemorrhage (IPH): Bleeding within the cerebral matter (brain parenchyma), not involving the ventricles

  *Acute Ischemic Stroke with hemorrhagic transformations included in IPH will be explained in comments.

- **Sub Arachnoid Hemorrhage (SAH)**
    - A subarachnoid hemorrhage is bleeding into the subarachnoid space—the area between the arachnoid membrane and the pia mater surrounding the brain
- **Sub-Dural Hematoma (SDH)**
    - Subdural hematoma occurs when there is tearing of the bridging vein between the cerebral cortex and a draining venous sinus
- **Epidural Hematoma (EDH)**
    - A rapidly accumulating hematoma between the dura mater and the cranium

12.8.2 Device Specific Events

Any device-specific event (DSE) is any malfunction or deficiency of the device.

A device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance (ISO 14155:2011 3.15)

Malfunction is defined as failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions For Use of Clinical Investigational Plan (ISO 14155:2011 3.27).

All device-specific events must be reported to both the Sponsor and local authorities as required by governing law. If a device malfunction results in an adverse event for the subject, this adverse event will be considered reportable to the Sponsor.

12.8.3 Event Reporting

The Investigator is required to report all SAEs within 72 hours and any UADEs/USADEs 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. The investigator will also send all available supporting documentation (de-identified as to the subjects' identity).

As additional information becomes available, copies of that source documentation which contain significant information related to the event such as progress notes, consultations, nurse's notes, operative reports, imaging studies and subject summaries etc. are requested for a complete evaluation of the event.

In regard to subject deaths, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the Sponsor when available. Any other source documents related to the death should also be provided to the Sponsor. In the event that no source documents are available, the PI is requested to describe the circumstances of the subject's death in a letter, e-mail or other written communication.

UADEs/USADEs have expedited reporting requirements. Any event that meets the definition of UADE must be reported to FDA, all Investigators and reviewing IRBs within 10 working days after becoming aware of information that an UADE has occurred.

The site will notify the reviewing IRB within 10 working days after becoming of aware of the effect. The Sponsor will notify the all Investigators, IRBs and the FDA within 10 working days after first receiving notification of the event. In addition, the Sponsor will comply with Medical Device Reporting / MDR regulations where applicable.

12.8.4 Protocol Deviations

Reports of any deviation from the protocol conducted in an emergency situation, to protect the life or physical wellbeing of a subject, will be reported to the Sponsor and IRB as soon as possible, but no later than 5 days from the time of the event.

13. Risk Analysis

The Barrel® VRD is intended for patients who have a bifurcating aneurysm or aneurysm occurring at a branch and require embolization of an MCA or basilar aneurysm and protection of the parent vessel. The potential benefit of this interventional procedure includes facilitation of endovascular coiling of wide-neck intracranial, MCA or basilar

aneurysms with embolic coils, while ensuring patency of the parent vessel, and to potentially improve clinical outcomes. However, the benefit of the Barrel® VRD device has not been established.

Evidence from investigations involving laboratory animals has suggested that the Barrel® VRD is safe for clinical investigation. With any interventional procedure there are risks of serious complications, including death. The inclusion and exclusion criteria for this population have been carefully established to limit the risk of mortality. Potential risks associated with utilization of embolic coils within brain aneurysms should be discussed with the subject within the coiling procedure Informed Consent document.

It is expected that the fluoroscopy time of the procedure will be similar to the time required for other interventional neuroradiology procedures.

- Potential adverse events that may occur during or after a procedure placing this device include, but are not limited to:
    - Adverse reaction to antiplatelet/anticoagulation agents or contrast media
    - Air embolus
    - Allergic reaction/toxic effects
    - Bleeding
    - Coma
    - 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
    - Mass Effect
    - 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
    - Vessel occlusion
    - Vision impairment

As a result of some of these complications, the subject may require treatment.

Eligibility criteria for this trial exclude subjects who are at higher risk for anticipated adverse events. Physician training and careful application of the Barrel® VRD, with close subject monitoring after the procedure, will also help to minimize risks. Risks of infection and risks associated with the access site are minimized by standard hospital procedures. The investigational site will be selected based on proficiency in neurointerventional procedures.

Although there are no guaranteed benefits from participation in this trial, the Barrel® VRD may potentially facilitate endovascular coiling of a wide-neck, intracranial, bifurcating aneurysm and protect the parent artery by preventing coils from protruding into the parent artery. This study is justified in order to establish whether this device can be used safely and effectively in this patient population.

Alternatives to treatment with the Barrel® VRD include treatment with other currently marketed, vascular reconstruction devices or surgical clipping.

14. Administrative Procedures

14.1 Responsibilities

14.1.1 Investigator

The Investigator and study site are required to conduct the clinical investigation in accordance with the protocol, all applicable laws and federal regulations, and any conditions or restrictions imposed by the governing IRB (21 CFR 812, and 21 CFR 54).

14.1.2 Sponsor and Clinical Monitor

Medtronic is responsible as the Sponsor to ensure proper monitoring of the study. Ongoing monitoring visits of the investigational center will be conducted to compare the data recorded on the CRFs with the information contained in the subjects' hospital records. The Investigator will provide the monitor access to all necessary records to ensure the integrity of the data (21 CFR 812).

14.2 Protection of Human Subjects

Written informed consent, in accordance with applicable federal, state and study center regulations, shall be obtained from each patient, or from their legal guardian, prior to the investigational procedures. The Investigator will retain a copy of the signed informed consent document in each subject's record, and provide a copy to the subject. The Investigator shall not request the written informed consent of any subject, and shall not allow any subject to participate in the investigation before obtaining IRB approval.

Prior to starting the study, the Investigator will provide Medtronic with a copy of the Informed Consent Document approved by the IRB with documented evidence that the IRB has approved the protocol (21 CFR 50).

14.3 Ethical Conduct of the Study

This study is to be conducted in alignment with ethical principles that have their base in the Declaration of Helsinki concerning medical research in humans and applicable regulations.

The Investigator agrees by participating in the conduct of this protocol to adhere to 21 CFR 812, the instructions and procedures described, and to adhere to the principals of Good Clinical Practice.

14.4 Institutional Review Boards

The Sponsor and/or Investigator must submit this protocol to the appropriate IRB, and is required to forward to the Sponsor a copy of the written and dated approval.

The study (study number, protocol title, and version), documents reviewed (e.g. protocol, ICF, etc.) and the date of the review should be clearly stated on the written IRB approval/favorable opinion.

The study will not start at a site and subjects will not be enrolled until a copy of written and dated approval/favorable opinion has been received by the Sponsor.

Any amendment or modification to the protocol should be sent to the IRB. The IRB should also be informed of any event likely to affect the safety of subjects or the conduct of the study.

The ICF used by the Investigator for obtaining the subjects informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate IRB for approval/favorable opinion (21 CFR 56).

Any report of withdrawal of IRB approval will be submitted to the Sponsor within 5 working days.

14.5 Protocol Changes

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

14.6 Subject Confidentiality

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, Medtronic, or other health authorities if they inspect the study records. A report of this study may be published; however the subjects' identities will not be disclosed.

14.7 Study Data

The primary efficacy endpoint in this study is Raymond Grade I (100% aneurysm angiographic occlusion) at 12 months ± 8 weeks. The sample size is based on a review of the modern literature, where the composite percent total occlusion reported is 43%[8] (see Background and Statistical Analysis sections for more detail).

Secondary endpoints will be presented in descriptive terms with incidence and 95% confidence intervals.

Subject demographic and clinical characteristics across sites, including age, gender, baseline, modified Rankin Score, NIHSS score, and Raymond grade will be reported and compared to determine whether significant differences exist from site to site.

Study outcome data, Raymond grade at 12 months± 8 weeks, and the rate of clinically significant procedural complications will be presented for the study and stratified by each site. If there is a significant difference among sites, a separate analysis excluding outlier sites will be presented to support the primary analysis results. Each site will follow the same protocol, and no single site will be allowed to enroll more than 20% of the total subjects.

14.8 Documentation

14.8.1 Source Documents

Source documents may include a subject's medical record, hospital charts, clinic charts, the Investigator's study files, questionnaires, as well as the results of diagnostic tests such as laboratory tests, angiograms, x-rays, CT or MRI scans.

The following information should be included in the subject's study records:

- Subject's name and contact information;
- The study title/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 numbers;
- Dates of all visits;
- Lists of medications;
- Documentation of AEs;
- Date subject exited the study, and a notation as to whether the subject completed the study or discontinued, with the reason for early termination.

14.8.2 eCRF Completion

Study data will be collected using eCRFs and a 21 CFR Part 11-compliant electronic data capture system. 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 and approving 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 that will enter data into eCRFs will undergo appropriate training for use of eCRFs.

Further information regarding eCRF navigation and use may be found in the eCRF completion guidelines.

14.8.3 Study Summary

The Investigator is responsible for submitting a study summary to Medtronic within a short time after completion of the study, and for supplying this summary to the governing IRB.

14.8.4 Documentation Retention

All study-related correspondence, subject records, consent forms, records of the distribution and use of the investigational products, and copies of CRFs should be maintained on file.

The Investigator shall retain study documentation during the study and for a period of two (2) years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application.

Medtronic 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 (21 CFR 812.140).

14.8.5 Storage of Investigational Products

The investigational devices must be stored in a secure area and administered only to subjects enrolled in the study, at no cost to the subjects, in accordance with the conditions specified in this protocol. The Investigator must keep an accurate accounting of the number of units received, dispensed, and returned.

14.8.6 Data Safety Monitoring Board (DSMB)

The DSMB will be an independent group that will serve as a data monitoring committee to the Sponsor of this Study. The DSMB will be comprised of individuals who are independent of the investigational sites and of representatives from multiple disciplines including but not limited to neurology, biostatistics/epidemiology, neurosurgery and interventional neuroradiology.

In the safety monitoring role, this board shall provide recommendations to the Sponsor regarding stopping /continuing enrollment in the study. The DSMB will establish proposed monitoring criteria for the study and will establish any required analyses for assessing safety. The group will also establish a mission statement and operating procedures.

The DSMB will also advise the Sponsor concerning the content of interim reports and the analyses that are required for data interpretation.

14.8.7 Clinical Events Committee

A CEC will be in place for the study using a minimum of three (3) physicians knowledgeable in the appropriate disciplines and medical specialties pertinent to the disease state being evaluated in this clinical study. All AEs will be collected and documented prior to adjudication by the CEC. This committee will be responsible for the review and adjudication to the study endpoints of the following events reported by the site:

1. Neurological adverse events with a corresponding worsening of NIHSS
2. All Device related adverse events
3. All Procedure related adverse events
4. All SAEs
5. All Antiplatelet therapy related events

The CEC will independently adjudicate to specified endpoint event definitions, event relatedness, event severity, and event outcomes.

The CEC can request additional source documentation and any potential imaging obtained in support of the adverse event to assist with adjudication.

14.8.8 Monitoring

The Sponsor will be responsible for ensuring that monitoring will be done in accordance to applicable regulations and will be outlined in the study's Clinical Monitoring Plan. All monitoring personnel for this study will be qualified by training, education and/or experience to perform their respective tasks.

The primary contact for the study is:

Clinical Affairs
9775 Toledo Way
Irvine, CA 92618
Tel: (949) 837-3700

Study monitors will conduct site visits to ensure accuracy of data, timeliness of data submissions, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed Investigator agreement, and compliance with IRB conditions and guidelines. Any non-compliance with these items that is not adequately addressed by the PI/site staff is cause for the Sponsor to put the Investigator/site staff on probation or withdraw the Investigator/site staff from the study. Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

All subject treatment, follow-up visits and phone conversations/interviews are to be fully documented either on the source document worksheets or in the subject's medical records. All information entered onto the eCRFs will be verified against the source documents and subject's medical records. Additional subject medical record review may be required for AE adjudication. De-identified source documents may be photocopied, if required. The study monitor will also check the Investigator Site File (ISF) to ensure that all study-related documents are current.

14.9 Quality Control and Quality Assurance

14.9.1 Data Control

Every effort will be taken to ensure the accuracy and reliability of data including the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel before the study commences, and periodic onsite monitoring visits by the Sponsor as deemed appropriate by the Sponsor. Guidance for eCRF completion will be provided and reviewed with the study personnel prior to the start of the study. The Sponsor will review eCRFs for accuracy and completeness and any discrepancies will be resolved with the Investigator or designee, as appropriate.

14.9.2 Site Selection

The Sponsor or representative of the Sponsor will assess each potential site to ensure the PI and his/her staff has the facilities and expertise required for the study. Sites will be selected based upon a site assessment, appropriate facilities, and the qualifications of the Investigator(s). Individual Investigators will be evaluated by the Sponsor based on experience with the intended procedure(s) and ability to conduct the study according to the study protocol.

To participate, a site must have the following components:

- Previous experience with clinical research and coil embolization of intracranial aneurysms
- An Investigator trained and on either phantom or bench-top model of the Barrel® VRD under fluoroscopic visualization.
- Commitment from the participating physician to pursue details of any safety outcomes
- Commitment from the participating physician to enroll only patients meeting inclusion and exclusion criteria
- A dedicated study coordinator who can enter data and respond to queries.
- Ability to perform required clinical testing and study procedures
- Ability and willingness to provide the Sponsor's representatives access to the hospital records, study files, and subject files as they pertain to the study

14.9.3 Site Training

Each investigational site will be trained to the investigational plan. Investigator/Site Personnel will undergo training prior to performing any study-related procedures. All training must be documented. Training to the investigational plan will include the following topics:

- Study objectives
- Protocol review
- Delegation of authority for study-related tasks
- Informed Consent process, including any relevant IRB requirements; Confidentiality/HIPAA (Health Insurance Portability and Accountability Act of 1996)
- eCRFs and completion instructions
- Documentation of protocol deviations
- AE reporting
- Device-specific events reporting
- IFU of the Barrel® VRD and Reverse Medical® Detachment System
- Device tracking and accountability
- Responsibilities and obligations of the Investigator/staff
- General guidelines for good clinical practices
- Study documentation required (essential documents)

Existing study site personnel who have been delegated new tasks and new study site personnel will undergo training to the investigational plan, as appropriate.

14.9.4 Site Initiation

The Sponsor or a designated representative will conduct a training session with study Investigators and respective staff to review the protocol, eCRFs, the informed consent process, IRB involvement and guidelines, responsibilities and obligations, reporting requirements, and general guidelines for good clinical practices.

Prior to enrolling subjects at an investigational site, the following documentation must be provided to the Sponsor:

- IRB approval for the Investigational Plan
- IRB and Sponsor-approved ICF for the study
- Signed Clinical Study Agreement (CSA)
- Documentation that verifies the appropriate study staff has been trained on the protocol, eCRFs and study conduct.
- Financial Disclosure(s) for the PI and Sub-I(s)
- PI and Sub-I(s) curriculum vitae (CV)

14.9.5 Data Quality Assurance

ORACLE Clinical Remote Data Capture (OC/RDC) is the electronic data capture (EDC) system that will be used to support data collection for this study. Documentation pertinent to the use of the EDC system will be made available for use by appropriate site personnel. All individuals who will be expected to use the EDC system will be given adequate training necessary to perform their assigned tasks as described in (21 CFR 11.10). Training will be conducted by qualified individuals and on a continuing basis, as needed.

14.9.6 Data Handling

The Sponsor is responsible for compilation and verification of the study data, retention of the clinical study database, performance of statistical analysis, and preparation of the study reports. The Sponsor will ensure that the performance of data management activities occur in accordance with the study data management plan.

14.10 Publications

The Sponsor intends to publish the results of this multicenter study. Individual investigators are therefore asked to refrain from reporting results from their study participants prior to publication of the main multicenter report. The Sponsor will establish authorship criteria for such publications for the study group, based on the study conduct and compliance, contribution to the study design, management or enrollment, and willingness to accept the rights and responsibilities of an author. The Sponsor will enter the study into a public clinical trials repository such as ClinicalTrials.gov.

15. References

The complete articles referenced in this protocol are provided in the Report of Prior Investigations section of this IDE application, along with additional articles relevant to treatment of intracranial aneurysms.

1 Molyneux, A. *et al.* International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* **360**, 1267-1274 (2002).

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14 Rezek, I., Mousan, G., Wang, Z., Murad, M. H. & Kallmes, D. F. Effect of core laboratory and multiple-reader interpretation of angiographic images on follow-up outcomes of coiled cerebral aneurysms: a systematic review and meta-analysis. *AJNR Am. J. Neuroradiol.* **34**, 1380-1384, doi:10.3174/ajnr.A3398 (2013).

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