Statisical Analysis Plan

The REVEAL Study

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Revision History

Version Number	Version Date	Affected Section(s)	Summary of Revisions Made:
1.0	14-AUG-2017	Original	Initial Release
2.0	01-AUG-2019	3.2, 3.3, 4.5	Correction to eligibility criteria for Per Protocol analystic subset; Increase in number of sites from 12 to 18; Correction to performance goals.

Contents

ABBREVIATIONS AND ACRONYMS

Acronym	Description
ABI	Ankle-brachial index
CEC	Clinical Events Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
ITT	Intention-to-Treat
LCL	Lower confidence limit
MAE	Major adverse event
MLD	minimum luminal diameter
PAD	peripheral arterial occlusive disease
PG	Performance goal
PP	Per Protocol
QVA	Quantitative Vascular Angiography
RVD	Reference vessel diameter
SAP	Statistical Analysis Plan
SFA	Superficial femoral artery
TBI	Toe-brachial index
TLR	Target lesion revascularization
TVR	Target vessel revascularization

1. INTRODUCTION

Infrainguinal peripheral arterial occlusive disease (PAD) is manifest over a spectrum of clinical presentations, ranging from the asymptomatic loss of peripheral pulses, leg claudication, to pain at rest, gangrene and limb-loss. The magnitude of signs and symptoms is well correlated with the anatomic extent of disease. Single-level, short arterial obstructions with moderate levels of stenosis may remain asymptomatic, while multilevel, long-segment occlusions often culminate in ischemic complications that threaten the viability of the limb.

The Rex Medical Revolution™ peripheral Atherectomy System is intended for use in peripheral vessels of suitable patients with atherosclerotic PAD.

1.1 Design, Treatments and Visits

The Reveal study is a multi-center prospective, non-randomized, single arm study and will enroll up to 121 subjects with PAD and significant target lesions of the appropriate diameter, located within the superficial femoral artery (SFA), popliteal and tibial arteries.

Data will be collected at baseline (screening), index procedure, hospital discharge, 1-month post index procedure and 6-months post index procedure. And adverse events will be collected at the index procedure, hospital discharge and through 6 months. Rutherford category, ankle-brachial or toe-brachial index and duplex ultrasound (DUS) of the target vessel will be collected at 1 month and 6 months.

1.2 Objectives

The purpose is to evaluate the safety and effectiveness of the Revolution™ Peripheral Atherectomy System in the treatment of infrainguinal lower extremity peripheral arterial occlusive disease.

Safety will be evaluated by assessing freedom from 30-day Major Adverse Event (MAE), defined as the composite of all-cause mortality, clinical-drive target lesion revascularization (TLR), major target limb amputation, major target vessel perforation requiring surgical or endovascular repair and clinically-significant distal embolization in the target limb as adjudicated by the independent Clinical Events Committee (CEC).

Effectiveness will be evaluated by acute debulking, assessed by technical success (≤50% diameter stenosis) after atherectomy with the study device, prior to adjunctive therapy with balloon angioplasty, stent deployment or other interventions. Effectiveness will be evaluated from post-atherectomy contrast angiograms, as evaluated by the independent core laboratory. Effectiveness will be assessed for all investigator-identified target lesions and calculated as the proportion of investigator-identified target lesions with technical success.

1.3 Randomization

This is not a randomized study.

2. ENDPOINT DEFINITIONS

2.1 Primary Safety Endpoint

The primary safety endpoint is a composite endpoint triggered by the occurrence of any five categories of events through 30 days after the index procedure[1]. These events are the following:

1. All-cause mortality- Death from any cause, from the point of enrollment through 30 days.

2. Clinically-driven TLR- Any revascularization of the target lesion that occurs after the subject has left the procedure room following the index procedure. TLR do not include adjunctive interventions performed during the index procedure, whether planned or for failed atherectomy or for complications of atherectomy. TLRs are considered to be clinically-driven when they occur as a result of restenosis >50% diameter reduction as measured angiographically or by duplex ultrasound (occlusion or stenosis with Peak Systolic Velocity Ratio >2.4)[2].

3. Perforation of the target vessel-Imaging evidence (standard contrast angiography, computed tomography angiography or open surgical/pathology visualization) of target vessel perforation from any cause. For angiography and CTA, perforation is defined by contrast extravasation outside of the adventitia.

4. Clinically- significant distal embolization- Target limb embolization documented on core laboratory- assessed angiography or with open surgery/pathology, accompanied by symptoms referable to the involved vascular bed.

5. Major amputation- Amputation of the target limb that results in limb shortening; i.e. is performed at or above the level of the malleoli.

The composite endpoint and each individual component are all subject level endpoints.

[1] The index procedure is considered to occur on day 0; the first post-procedure day is day 1, and so on. The 30-day time point includes any events with a start date prior to 11:59PM on day 30.
[2] If an angiogram and a duplex ultrasound imaging study are discordant within any 30-day period, the angiographic results will supersede the duplex findings.

2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is technical success defined as acute debulking resulting in a reduction of stenosis to ≤50% after treatment with Revolution™ Peripheral Atherectomy System from baseline and prior to other adjunctive therapies at the conclusion of the index procedure, as measured by angiographic core laboratory.

Within any target lesion, stenosis is measured at the point of the minimum luminal diameter (MLD) over its shoulder -to – shoulder length[3]. The reference vessel diameter (RVD) is the interpolated diameter from the point just proximal to the point just distal to the target lesion. The percent stenosis is calculated as:

% Diameter Stenosis=1-MLD/RVD.

This is a lesion level endpoint.

2.1 Secondary Endpoints

Secondary endpoints will consist of the following with level of analysis in parentheses:

1) Change in percent stenosis after treatment with Revolution™ Peripheral Atherectomy System, determined after atherectomy and prior to other adjunctive therapies, as measure by the angiographic core laboratory (lesion level);

2) Procedural success as defined by target lesion residual stenosis of <30% at the conclusion of the index procedure, after atherectomy and any adjunctive endovascular treatment, as measured by the angiographic core laboratory (lesion level);

3) Assessment of the individual components of the primary safety endpoint (MAE); including all-cause mortality, major target limb amputation, clinically significant distal embolization, major target vessel perforation requiring surgical or endovascular repair, and clinically-driven TLR, measure through 30 days and at 6 months (subject level);

4) Minor unplanned target limb amputation rate through 30 days and 6 months (subject level);

5) Myocardial infraction through 30 days and 6 months (subject level);

[3] The shoulder-to-shoulder length is determined visually using a Quantitative Vascular Angiography (QVA) software application. RVD is determined at the location of the MLD, linearly interpolated between the luminal diameters just proximal to and distal to each shoulder.

6) Incidence of target vessel revascularization (TVR) through 30 days and 6 months (subject level);

7) Frequency of angiographic procedural distal embolization (symptomatic) in the target limb as confirmed angiographically by the core laboratory (subject level);

8) Primary patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography (subject level);

9) Primary-assisted patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography (subject level);

10) Secondary patency of the target lesion at 30 days and 6 months, determined by duplex ultrasound or angiography (subject level).

3. ANALYSIS POPULATION

The point of enrollment in this study occurs when a study device first enters a subject's vasculature.[4] The following populations will be analyzed in the study:

3.1 Intention-To-Treat (ITT) Analysis

The ITT analysis will be performed on all enrolled subjects in whom the study device entered the vasculature, irrespective of adherence with the entry criteria, treatment actually received, subsequent withdrawal, or deviation from the investigational plan. Analysis of safety outcomes will use the ITT population.

3.2 Per Protocol (PP) Analysis

The PP analysis will be performed on target lesions with core laboratory determined RVD falling within the pre-specified anatomic eligibility criteria of ≤ 4.0 mm. The effectiveness endpoints will be determined using the PP analytic subset to exclude lesions where the largest bore (2.0 mm) study device is less than 50% of the RVD. The per protocol population has no other pre-specified inclusion/exclusion violations(s) or requirement for adequate follow-up (or a loss of patency).

3.3 Sample Size Consideration

This study will enroll up to 121 subjects at up to 18 investigational sites and the sample size estimation was based on binomial hypothesis testing of a single proportion.

The performance goal (PG) of 80% has been established for the primary safety endpoint. Sample size estimation was based on a one-sided 97.5% exact binomial test. The 30-day

[4] This point is defined as entry of the study device into the access sheath/guide at the level where the sheath/guide enters the subject's body.

MAE rate is anticipated to be approximately 9%. Under these assumptions, the required sample size to achieve a level of 90% power is 110 subjects (Table 1). Assuming 10% attrition over 30 days, initial enrollment of 121 subjects is necessary.

A PG of 76% has been established for the primary effectiveness endpoint. Anticipating an actual technical success rate of approximately 86%, and based upon a one-sided 97.5% exact binomial test, the required sample size to achieve a level of 90% power is 165 target lesions. Assuming a 1.5 ratio of subjects to treated target lesions, approximately 110 subjects will be necessary (Table 2). Since the primary effectiveness endpoint is determined at the time of the index procedure, no attrition has been taken into account.

Table 1. Sample Size – Primary Safety Endpoint

Primary Safety Endpoint	
Performance goal	80%
Anticipated freedom from MAE	91%
Significance level	.025
Statistical test	One-sided exact binomial test
Desired power level	90%
Required sample size prior to attrition (subjects) adjustment*	110
Required sample size after attrition rate adjustment	121
**Assumes 10% 30-day attrition*	

Table 2. Sample Size – Primary Effectiveness Endpoint

Primary Effectiveness Endpoint	
Performance Goal	76%
Anticipated technical success rate	86%
Significance level	.025
Statistical test	One-sided exact binomial test
Desired power level	90%
Required sample size (target lesions)	165
Estimated subjects required for required number target lesions*	110
**Assumes 1.5 target lesions treated/subject; ratio calculated from atherectomy literature review.*	

4. STATISTICAL METHODS OF ANALYSIS

4.1 Statistical Methodology

The objective of the statistical design for this study is to evaluate the safety and effectiveness of the study device, as assessed in comparison to literature-derived performance goals.

The safety and effectiveness performance goals were determined from a literature review of atherectomy publications. A total of 19 studies were included in this review and, among these, 13 reported data referable to the primary safety endpoint and 7 reported data referable to the primary effectiveness endpoint. Studies with populations that overlapped the population of another study were excluded. See the study protocol for more details on the results of the literature review on primary safety and effectiveness endpoints.

4.2 Baseline Comparability

Poolability of data across clinical study sites is justified on a clinical basis (i.e. all study sites use the same protocol) the sponsor monitors the site for protocol compliance, and the data gathering instruments are identical. The Food and Drug Administration (FDA) also requires a statistical assessment of poolability. This is done by comparing the baseline characteristics across study sites. For categorical baseline variables, such as sex, a generalized Fisher's exact test or equivalent test will be used and for quantitative variables, parametric or non-parametric analysis of variance (general linear models or an equivalent procedure) will be used.

The above statistical analyses do not result in an impediment to pooling, but rather assess the balance of baseline covariates across study sites. If any baseline covariate is found to be statistically significant by this process, multivariate analyses will be done to determine if imbalance affected study outcome. This is done by using both the variable found out of balance and study site as possible covariates.

It may be necessary to combine two or more low enrolling study sites into pseudo-sites to allow these analyses. Sites with fewer than 6 subjects will be ranked by enrollment low to high. Starting from the lowest enrollment sites, sites will be combined into a pseudo sites until the combined size reaches the median enrollment among all sites. This process will be repeated until all resulting sites have enrollment equal to or greater than 6 subjects. This will be done in a manner to preserve the structure of the study and prevents bias.

Baseline characteristics to be considered as possible covariates are as following:

- Age
- Sex
- Coronary artery disease
- Chronic obstructive pulmonary disease
- Myocardial infarction
- Hyperlipidemia
- Cerebrovascular accident
- Hypertension
- Diabetes
- History of tobacco use
- History of peripheral vascular disease
- Rutherford Category
- ABI/TBI

If there are relatively few missing data points (e.g., <10%) for a given variable, a simple sex-specific imputation using the mean (for continuous variables) or median (for dichotomous or categorical variables) of the non-missing values will be done. If there are >10% missing, the variable will be excluded from the imputation analysis.

Poolability analysis will also be performed on the primary endpoints comparing across sites after adjusting for covariates difference. Logistic regression models will be utilized to include unbalanced covariates and site as an independent variable and the study outcome as dependent variable to assess outcome difference. If the p-value of site effect is less than 0.10, further analyses will be undertaken to investigate the imbalance of the study outcome.

4.3 Effectiveness Analyses

The primary effectiveness endpoint is technical success, defined by ≤50% diameter stenosis after atherectomy with the Revolution™ Peripheral Atherectomy System, prior to adjunctive therapy, as measured by the independent core laboratory on the post-atherectomy contrast angiogram. Effectiveness will be assessed for all investigator-identified target lesions in the PP analytic group and will be calculated on per-lesion basis.

H_0: $P_E \leq PG_E$ versus H_A: $P_E > PG_E$

Where P_E is the proportion of subjects with technical success, as defined by angiographically-determined ≤50% target lesion diameter reduction on the post-

atherectomy core laboratory measurement[5]. The effectiveness performance goal, PG_E, is technical success defined in the same manner, derived from the published literature.

The primary effectiveness endpoint will be calculated for those PP target lesions that fall at or below the specified acceptable reference vessel diameter of 4.0 mm, as determined by the core laboratory. Target vessels with diameters < 2.0 mm and > 4.0 mm will be excluded from the analysis, since even the largest bit size (2mm) would not result in a post-atherectomy channel size of ≥50% RVD. For subjects with >1 lesion, it is possible that one vessel qualifies for the PP analysis with RVD ≤ 4.0 mm and others do not, with RVD >4.0 mm. For lesion level effectiveness endpoints, only PP qualifying lesions will be included in the analysis. For subject level effectiveness endpoints, subjects with nonqualifying PP lesion(s) will be excluded from the analysis.

It was originally planned for the primary effectiveness endpoint analysis to use the E+M approach for one sample correlated binary data with cluster size of one or two that accounts for correlations between multiple target lesions within the same subject[5]. However, based on a recommendation from FDA the primary analysis method was changed to generalized estimating equations (GEE). FDA also recommended assessing the power of this analysis using this method, however, it was determined that information needed for the assumptions required was not available, e.g. the correlation between lesions within a subject.

4.4 Safety Analyses

The primary safety endpoint for this study is a composite endpoint of any MAE through 30 days, as adjudicated by the CEC. MAE is defined as 30-day all-cause mortality, clinically-driven TLR, major target limb amputation, major target vessel perforation requiring surgical or endovascular repair and clinically-significant distal embolization in the target limb. The rate of MAE will be compared to a performance goal with the following null and alternative hypotheses:

H_0: $P_S \leq PG_S$ versus H_A: $P_S > PG_S$

where Ps is the proportion of subjects free from MAE through 30 days and PG_S is the safety performance goal derived from the studies reporting the elements contained in the composite MAE endpoint.

The Exact binomial one-sided 97.5% confidence interval will be used to test the primary safety endpoint.

[5] Technical success is defined on the post-atherectomy angiogram, prior to adjunctive therapy with balloon angioplasty, stent deployment, or any other intervention.

4.5 Study Success Criteria

The study will be considered a success if both the primary endpoints meet their respective Performance Goals. For the effectiveness endpoint, this translates into observing a one-sided 97.5% lower confidence limit (LCL) of the point estimate above 76% and for the safety endpoint it means observing a one-sided 97.5% LCL above 80%.

4.6 Additional Analyses

4.61 Demographics and Baseline Characteristics

The baseline demographics and anatomic characteristics of the treatment group will be presented with descriptive statistics.

4.62 Changes to Planned Analyses

All analyses will be detailed in the Statistical Analysis Plan (SAP). Any changes to the planned analyses will be documented as amendments to the SAP and in the study report.

4.63 Interim Analyses

The Data Safety Monitoring Board (DSMB) will review safety data (including components of the primary effectiveness endpoint, since these may impact safety) to ensure that it is ethical to continue the study based on the absence of unacceptable risks to the subject.

There will be a descriptive safety and effectiveness analysis of the primary endpoints after 25 subjects have reached the 30 days Follow-Up milestone by independent statisticians. Enrollment will not stop during this analysis. The results of this analysis will not be made public before the formal primary endpoint analysis and may be used for regulatory submission(s) outside of the US.

4.64 Subgroup Analyses

Subgroup analyses will be performed on target lesions of the superficial femoral, popliteal and tibial arteries. Additional subgroup analyses are planned for gender, diabetes mellitus, Rutherford Class, Age 75 years cutoff, lesion length tercile, and chronic total occlusion. The analyses will comprise descriptive analyses of the primary and secondary effectiveness endpoints.

4.65 Univariate/Multivariate Analyses

Univariate and multivariate predictor analyses will be carried out on the primary endpoints using logistic regression.

4.66 Survival Analyses

Survival analyses will be carried out on the time to event outcomes using Kaplan-Meier plots and lifetable analyses.

4.7 Missing or Incomplete Data

Every effort will be made to minimize the amount of missing data. Recognizing the difficulty of avoiding some missing data, however, data imputation methods with sensitivity imputation analyses will be carried out. Safety endpoint analysis will include all subjects experiencing at least one component for the safety endpoint or with follow-up to the lower limit of the follow-up window for each time point, i.e., the denominator will be adjusted for missing data. Subjects with missing effectiveness data for target lesions (MLD at the conclusion of atherectomy) will be assumed to have missing data at random and will be imputed by random selection with replacement of data from target lesions with post-atherectomy measurements. The robustness of the multiple imputation outcome will be tested with a tipping point analysis encompassing all possible imputation outcomes.

5. ENDPOINT ALGORITHMS

5.1 Safety Endpoints

For missing values, an adjustment to the denominator will be made based on the amount of evaluable data for safety-endpoints.

Safety denominator adjustment: For each visit (or reporting time point), the event rate will be calculated as the number of subjects with certain event term over the number of evaluable subjects. The evaluable subjects at each reporting time point include all subjects who are enrolled by the snapshot date and

1) Had an event within (on or before) the reporting cutoff days, or
2) Had a follow-up at or after the lower limit of the reporting window, or
3) The withdrawal consent date/recorded lost-to-follow-up date at or after the lower limit of the reporting window

'Days to event' (date of earliest event – date of index procedure) and 'Days to last contact' (date of last contact – date of index procedure) are usually used for the determination of the eligibility of the 'evaluable subject'. The last contact date will be calculated based on the information gathered from all available dates during the follow-ups.

The 'Reporting Cutoff Days', 'Lower limit of the Reporting Window' and the correspondent visits are as the following:

Visit	Reporting Cutoff Days	Lower Limit of the Reporting Window (days post-index procedure)
1-month	30 days post-index procedure	Days to last contact: 23
6-month	180 days post-index procedure	Days to last contact: 166

5.2 Effectiveness Endpoints

Patency effectiveness endpoints (site-reported endpoints) include the endpoints that are determined by site assessment (DUS or angiography), such as the significant stenosis/occlusion measured by DUS or angiography as well as consideration of the clinical endpoint – TVR. Such site-reported endpoints rely on the actual evaluable assessment. If the scheduled assessment is not completed or the data is not evaluable (i.e., not readable, or non-diagnostic), it will be treated as missing value and will be excluded from the analysis.

The significant stenosis component for the patency endpoints (primary patency and primary-assisted patency) is determined by a qualified angiogram diameter stenosis (DS) ≥ 50% and <100% evaluated by the site or qualified DUS evaluated as DUS category '50-99%' that is evaluated by the site-reported DUS. The occluded component of primary and secondary patency endpoints is determined by a qualified angiogram DS=100% or qualified DUS evaluated as 'occluded'. Either significant stenosis or occlusion will be considered failure of primary patency.

Data will be used for subjects who have an evaluable (readable or diagnostic) scheduled or unscheduled DUS or angiographic assessment (site-reported imaging assessments) that will be based on reporting windows described below. To minimize the missing assessment at 1 and 6-month visits, analysis windows provided below will be utilized.

Given that angiography is a more precise visualization of the vessel than DUS, in cases where both angiography and DUS are available at the same assessment and they provide different conclusions then angiography will be preferentially used in the algorithm.

Step 1. For convention, the imaging visits use the following reporting windows. The study day used in the window definitions is calculated as "assessment date" minus "Index procedure date":

Study Visit	Target Day	Compliance Reporting Windows	Analysis Reporting Windows
Index Procedure	Day 0	N/A	N/A
Discharge	Discharge	N/A	1-discharge
30-days	Day 30	Study Day 23 – 37	15-60
6-month	Day 180	Study Day 166 – 194	61-210

These reporting windows serve 2 primary functions:

1) Allow for the calculation of compliance to imaging follow-up for each visit – compliance reporting window ranges.
2) Provide the analysis reporting windows for patency endpoints at key follow-up time points.

Step 2. If the scheduled assessment is not completed or is not evaluable (i.e. not readable or non-diagnostic), this assessment will be censored (or excluded from proceeding to the next step).

Step 3. If a visit has multiple DUS or angiographic assessments, the following hierarchical criteria will be used to identify the appropriate assessment for that visit:

- Choose the one that has a positive observation(s) – i.e. significant reduction of blood flow, etc.; if more than one assessment contains at least one positive observation, the earliest assessment will be used;
- If none of the assessments has positive observations, choose the one that is the closest to the scheduled visit date

Step 4. If a visit has both DUS assessment and angiographic assessment, the following hierarchical criteria will be used to identify the appropriate assessment for that visit to use in the analysis:

- If there are multiple DUS assessments or multiple angiographic assessments that are slotted in the same visit window, please refer to step 3 to select one non-missing assessment for DUS and/or angiography separately. Please refer to the following table for the assessment and outcome determination

DUS assessment	Angiographic assessment	Final selected assessment	Final selected assessment outcome
Success	Failure	Angiography	Failure

Success	Success	Choose the one that is the closest to or earlier than the scheduled visit date	Success
Success	Missing	DUS	Success
Failure	Failure	Choose the one that is the closest to or earlier than the scheduled visit date	Failure
Failure	Success	Angiography	Success
Failure	Missing	DUS	Failure
Missing	Failure	Angiography	Failure
Missing	Success	Angiography	Success
Missing	Missing	N/A	Missing

As stated previously and shown in the hierarchy above, in cases where both angiography and DUS are available at the same assessment and they provide different conclusions then angiography will be preferentially used.

The step-by-step description of the above hierarchical criteria in determining the 1 and 6-month site assessments is as follows:

1) Remove the assessments with value of 'N/A' or 'missing'. If the assessment result is N/A or missing, then delete (e.g., set the value to 'missing');
2) Data will be used for subjects who have an evaluable (readable) scheduled or unscheduled DUS or scheduled or unscheduled angiography. Failure of patency can occur at any time post-procedure. Choose the first occurrence of angiography for failure. If no angiography failure, then choose the first occurrence of DUS failure. If there are no failures, but there are success(es) then choose the last successful occurrence of angiography and if no angiography then use the last successful occurrence of DUS. If there are no DUS or angiography assessments, then set the value to 'missing'.

5.21 Primary Patency

Censor any DUS or angiogram assessments taken after any TVR as a revascularization changes the vessel making it unevaluable. If the date of assessment > date of TVR, then delete (e.g., set the value to 'missing').

At the time of a CD TLR set primary patency to failure.

Once a failure of primary patency has occurred in a subject all future time points reporting primary patency will be set to failure. If there are no failures and one or more successes, then the subject is a success up to the time of the last success recorded.

Unique composite endpoint such as primary patency contains both site-reported imaging endpoint and clinical/safety endpoint (by cut-off days), the event of the

individual components will be determined first, and the composite endpoint will then be determined as the following:

Freedom from significant stenosis/occlusion within 1-Month	Freedom from CD TLR within 37 Days	1-Month Primary Patency
Yes	Yes	Yes
Yes	No	No
Yes	Missing Data	Missing Data
No	Yes	No
No	No	No
No	Missing Data	No
Missing Data	Yes	Missing Data
Missing Data	No	No
Missing Data	Missing Data	Missing Data

Primary Patency at 6 months follow-up will be determined following similar convention specified above for 1 month.

5.22 Primary-assisted Patency

If a subject is a success on primary patency, then they are a success on primary-assisted patency and require no further evaluation via this algorithm. If a subject is a failure on primary patency without a subsequent TVR then they are a failure on primary-assisted patency and require no further evaluation via this algorithm. Subjects failing primary patency for a significant stenosis diagnosed via imaging and undergoing a TLR will be assessed following the TLR for primary-assisted patency by the algorithm below.

Unique composite endpoint such as primary-assisted patency contains both site-reported imaging endpoint and clinical/safety endpoint (by cut-off days), the event of the individual components will be determined first and the composite endpoint will then be determined as the following (apply to primary patency failure subjects following TLR for significant stenosis only):

Freedom from significant stenosis/occlusion within 1-Month	Freedom from 2nd CD TLR within 37 Days	1-Month Primary-assisted Patency
Yes	Yes	Yes
Yes	No	No
Yes	Missing Data	Missing Data
No	Yes	No

Freedom from significant stenosis/occlusion within 1-Month	Freedom from 2nd CD TLR within 37 Days	1-Month Primary-assisted Patency
No	No	No
No	Missing Data	No
Missing Data	Yes	Missing Data
Missing Data	No	No
Missing Data	Missing Data	Missing Data

Once a failure of primary-assisted patency has occurred in a subject by the algorithm above then all future time points reporting primary-assisted patency will be set to failure. If there are no failures and one or more successes, then the subject is a success up to the time of the last success recorded.

Primary-assisted patency at 6 months follow-up will be determined following similar convention specified above for 1 month.

5.23 Secondary Patency

If a subject is a success on primary patency, then they are a success on secondary patency and require no further evaluation via this algorithm. If a subject is a failure on primary patency without a subsequent TVR then they are a failure on secondary patency and require no further evaluation via this algorithm. Subjects failing primary patency and undergoing a TLR for total occlusion diagnosed via imaging will be assessed following the TLR for secondary patency by the algorithm below.

Unique composite endpoint such as secondary patency contains both site-reported imaging endpoint and clinical/safety endpoint (by cut-off days), the event of the individual components will be determined first and the composite endpoint will then be determined as the following (apply to primary patency failure subjects following TVR for total occlusion only):

Freedom from significant stenosis/occlusion within 1-Month	Freedom from 2nd CD TLR within 37 Days	1-Month Secondary Patency
Yes	Yes	Yes
Yes	No	No
Yes	Missing Data	Missing Data
No	Yes	No
No	No	No
No	Missing Data	No

Freedom from significant stenosis/occlusion within 1-Month	Freedom from 2nd CD TLR within 37 Days	1-Month Secondary Patency
Missing Data	Yes	Missing Data
Missing Data	No	No
Missing Data	Missing Data	Missing Data

Once a failure of secondary patency has occurred in a subject by the algorithm above then all future time points reporting secondary patency will be set to failure. If there are no failures and one or more successes, then the subject is a success up to the time of the last success recorded.

Secondary patency at 6 months follow-up will be determined following similar convention specified above for 1 month.

5.24 Endpoint Assessed by Office Visit

Such endpoints include WIQ Scores, etc. These assessments /endpoints are obtained/determined through the office visit assessment. If the office visit is not completed then these assessments will not be available, and therefore will be treated as missing values and will excluded from the analysis.

For the assessments that are recorded on the scheduled visits forms, the scheduled visit number will be used in the analyses.

For subjects that don't have any assessment for a scheduled visit (visit not done or the visit is completed by the assessment is not readable), the following rules will be used to slot the unscheduled visit assessments:

1) Assessments will be slotted into each study visit (including scheduled and unscheduled visit) using the visit date, visit window is described in previous section;
2) The assessments with unevaluable values will be excluded from the visit slotting step;
3) If multiple assessments are slotted into the same visit window, the assessment with non-missing value that is closet to or earlier than the scheduled visit date will be used. If multiple non-missing assessments have equal distance from the scheduled visit date, the assessment from the earlier assessment will be used.