STATISTICAL ANALYSIS PLAN

The "RADIANCE-II" Pivotal Study

A Study of the ReCor Medical Paradise System in Stage II Hypertension

(CLN 0841 / CLN-0863)

Revision A

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Author: Chris Mullin, M.S.

NAMSA

ReCor Medical Inc. 1049 Elwell Court Palo Alto, CA 94303 USA	**CONFIDENTIAL** – This document contains confidential information that is the property of ReCor Medical Inc. It may not be reproduced or disclosed without the express written consent of ReCor Medical.	ReCor Medical BV. Keizersgracht 482 1017EG Amsterdam, The Netherlands	ReCor Medical Ltd. 46 Innovation House Discovery Park, Innovation Way Sandwich, Kent CT13 9FF United Kingdom

REVISION HISTORY

Revision #	Release Date	Description
01	25-SEP-2019	Initial Release.
02	19-NOV-2020	Added mitigations and sensitivity analyses related to missing data and COVID-19 (i.e. multiple imputation, poolability of pre/post COVID-19 cohorts, etc.), additional minor details for analyses and organizational edits.
A	03-MAY-2022	Update to reflect the number of randomizations needed to yield the target evaluable sample population at 2-months based on actual attrition rate; minor clarifications throughout.

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1. PURPOSE

This Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under the ReCor "RADIANCE-II" Study, and details on specific planned pooled analyses across the RADIANCE studies.

2. SCOPE

This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the plan has been developed with respect to the ReCor RADIANCE-II Study protocol (applicable versions listed under Section 3, Applicable Documents). Relevant changes to the protocol or eCRF may necessitate updates to the SAP. This SAP supersedes the study protocol.

3. APPLICABLE DOCUMENTS

Document Number (Rev)	Document Title
CLN-0841 (Revision D)-US CLN-0863 (Revision D)-EU	ReCor RADIANCE-II Study Protocol
CLN-0030 (Revision A)	ReCor RADIANCE HTN Statistical Analysis Plan
NAMSA STATSOP-002	Statistics Standard Operating Procedure – Statistical Analysis Plan

4. SOFTWARE

All tables, listings and figures will be produced using SAS Version 9.4 (SAS Institute, Cary, NC.) or a later version of SAS, R, Excel, or other validated software system.

5. TRIAL OBJECTIVES

The objective of the RADIANCE-II study is to demonstrate the effectiveness and safety of the Paradise System in subjects with Stage 2 hypertension on 0-2 medications at the time of consent. Prior to randomization, subjects will be hypertensive in the absence of hypertension medication.

6. TRIAL DESIGN

RADIANCE-II is a randomized, double-blind, sham-controlled, single cohort study designed to demonstrate the effectiveness and safety of the Paradise Renal Denervation System in hypertensive subjects.

6.1 Randomization

A 2:1 randomization scheme will be used to assign subjects to treatment or blinded control (sham). Randomization will be generated by computer and stratified by center using blocks of small size and treatment permutation. Randomization will occur immediately following the renal angiogram to maintain subject blinding and to allow that subjects may be excluded prior to randomization for reasons of unsuitable renal anatomy.

6.2 Blinding

The subjects and all study personnel taking follow-up BP measurements post-discharge through 12 months follow-up will be blinded to the randomization. Subjects will complete a blinding assessment post-procedure but prior to hospital discharge, at 2 months, at 6 months, and at 12 months follow-up.[1,2] All ABP measurements are uploaded to the dabl ABPM core lab and are be evaluated blinded to randomization.

6.3 Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or for futility. Interim datasets will be provided to the DSMB for the purposes of review of safety.

7. SAMPLE SIZE CONSIDERATIONS

The sample size for the study is based on a desire to compare randomized groups at the point of the Primary Efficacy Endpoint. Calculations are based on evaluating the treatment versus control groups.

Statistical analyses will be performed at a two-sided 0.05 alpha level. Conservatively, sample size calculations are based on a two-sample t-test. The planned analysis with the adjustment for baseline should provide additional power beyond this, but the precise level depends on the correlation of the baseline value with the reduction during FU. Based on a 2:1 randomization, two-sample t-test, for an assumed mean ± standard deviation difference of 6±12 mmHg, a planned evaluable sample size of 192 subjects will provide 90% power. These calculations can be confirmed with the following SAS System (version 9.4) code:

```
proc power;
twosamplemeans test=diff
meandiff = 6
stddev = 12
alpha = 0.05
power = 0.90
groupweights = (2 1)
ntotal = . ;
run;
```

To account for the loss of power due to missing data at the 2 month FU visit, and a desire to have sufficient subjects for meaningful pre-specified cohort analyses of efficacy, an estimated 15% inflation was used to calculate the initial number of randomized subjects of 225.

Based on a blinded assessment of the missing data rate for the 2 month FU visit, the rate of missing data was 2.3%. Assuming a somewhat more conservative rate of 4%, it is expected that 200 randomized subjects are needed to yield the required 192 evaluable subjects.

The primary safety endpoint will be compared to a pre-specified performance goal of 9.8%. The percentage of subjects who experience a primary safety endpoint will be reported along with the corresponding upper one-sided exact 95% confidence bound. The estimated sample size of 128 treated subjects should provide 95% power for the performance goal if the population safety rate is approximately 3.0%.

8. STATISTICAL ANALYSES

8.1 General Considerations

Continuous measures will be summarized with sample size, mean, median, standard deviation, minimum and maximum; categorical measures will be presented with the counts and percentages of subjects in each category.

The date of the subject's procedure will be considered study day 0.

8.2 Analysis Populations

The Intent-to-Treat (ITT) population will consist of all randomized subjects analyzed according to their original randomization assignment.

The modified Intent-to-Treat (mITT) population will consist of all randomized subjects analyzed according to their original randomization assignment, except will exclude subjects that met the protocol defined "High BP Action" (Section 8.12.1, Clinical Protocol) necessitating the re-start of anti-hypertensive medication prior to the 2-month primary endpoint.

The complete ABP (CA) population will consist of all randomized subjects analyzed according to their original randomization assignment that have ABP values at both baseline and follow-up.

The Per-Protocol (PP) population will include all subjects who are randomized, have treatment delivered successfully and are free from major issues which may affect the assessment of the treatment:

- Baseline daytime ABP <135/85mmHg or failure to obtain baseline ABP recording
- Renal artery anatomical exclusion deviations
- Failure to obtain 2 month follow-up ABP recording
- Subjects restarting antihypertensive medication, for any reason, prior to the 2-month primary endpoint.

The As-Treated (AT) population will consist of all randomized subjects analyzed according to their original randomization assignment except that subjects randomized to treatment who received no ablations will be excluded.

The Crossover (CO) population will consist of subjects who receive active treatment after being randomized to a control group. For the primary analyses of the ITT, mITT, PP, and AT populations, subjects randomized to the control group who crossover will be censored at the time of crossover. Crossover subjects will not be included in primary endpoint calculations beyond the point of censoring but may be combined with active subjects in supplementary analyses. These supplementary analyses will focus on the experience of crossover subjects after crossover, as appropriate comparing with the randomized treatment subjects.

The primary population for efficacy and safety analysis will be the intent-to-treat (ITT) population. As additional sensitivity analyses, the primary effectiveness analysis will be repeated for the mITT, CA, PP, and AT populations. Following 2 months, efficacy and safety analyses will be done based on evaluable data.

Note that the terms for subject classification defined in the protocol ("Screening Failure", "Attempt", and "Treatment" subjects, Section 7.4) differ both in definition and in purpose

to the use of these words for the purposes of statistical analyses. Statistical analyses will follow the definitions in this analysis plan.

8.3 Primary Efficacy Endpoint Analysis

8.3.1 Primary analysis

The mean difference between randomized groups for the change in daytime ambulatory systolic BP at 2 months post-procedure will be compared via a linear regression (ANCOVA) model adjusted for subjects' baseline daytime ambulatory systolic BP. In mathematical formulation, the statistical hypothesis test will be based on the following:

$$Ho: \beta_{txt} = 0$$

$$Ha: \beta_{txt} \neq 0$$

Where β_{txt} is the regression coefficient for the treatment versus control term from the following linear model:

$$Y = \beta_0 + \beta_{txt}*X_{trt} + \beta_{bl}*X_{bl}$$

Where

- Y = the reduction in ambulatory systolic BP from baseline to 2 months post-procedure
- β_{txt} = the regression coefficient associated with the treatment term
- X_{trt} = a indicator variable for treatment group, with a value of 1 for the treatment group and 0 for the control group
- B_{bl} = the regression coefficient associated with the baseline ABP
- X_{bl} = the baseline ABP

For patients that met the protocol defined "High BP Action" changes, the last blood pressure measurement prior to the medication change (i.e. the baseline value) will be used for the reduction in blood pressure in the analysis.

For patients with missing 2-month follow-up ABP values, multiple imputation will be employed. This will be based on a fully conditional specification using the following covariates for the imputation model: age, sex, and baseline ambulatory systolic BP. Imputation will be performed separately by randomized treatment group. If necessary, an augmented likelihood approach will be used to facilitate implementation of the imputation model. Twenty imputed data sets will be produced and combined via Rubin's rules[3] to produce the p-value for the primary efficacy endpoint test and the confidence interval for the treatment effect.

This ANCOVA model assumes a normal distribution of residuals. A Shapiro-Wilk test for normality will be performed at the 0.05 alpha level based on observed data. If there is significant evidence of non-normality, analysis will be based on ranking the observations (with no imputation) and applying the ANCOVA model to the ranked data as described Quade (1967), "Rank Analysis of Covariance", Journal of the American Statistical Association, Vol 62, No 320. The Hodges-Lehman estimator (and associated 95% confidence intervals) will also be used to describe the results.

8.3.2 Sensitivity Analysis

As a sensitivity analysis evaluating the effect of missing endpoint data, a tipping point analysis will be conducted. The tipping point analysis will evaluate best case, worst case, and multiple cases in-between. A subject with missing data will be imputed from a range of that subject's treatment group BP reduction percentile value: 0% (minimum), 25%, 50%, 75%, 100% (maximum). This will result in a 5x5 table with active treatment on one side and control on the other. Within each cell of the 5x5 table the endpoint results will be calculated, and consistency will be evaluated.

8.4 Secondary Efficacy Endpoint Analyses

The statistical analysis of the secondary efficacy endpoints will follow the methodology of the primary Efficacy Endpoint, including use of multiple imputation for missing data. For the purposes of controlling the type I error rate for inferential labeling claims for secondary endpoints, a sequential gatekeeping procedure will be employed, testing hypotheses for secondary endpoints at the 0.05 level until a non-significant result is produced, at which point testing for labeling claims will cease. The sequential testing order will be performed as follows:

- Reduction in average 24-hr ambulatory systolic BP at 2 months post procedure.
- Reduction in average home systolic BP at 2 months post procedure
- Reduction in average office systolic BP at 2 months post procedure
- Reduction in average daytime ambulatory diastolic BP at 2 months post procedure
- Reduction in average 24-hr ambulatory diastolic BP at 2 months post procedure
- Reduction in average home diastolic BP at 2 months post procedure
- Reduction in average office diastolic BP at 2 months post procedure

Note this ordering for the purposes of sequential gatekeeping differs from the order the secondary efficacy endpoints were originally listed in the protocol. This updated list is based on results from the RADIANCE HTN SOLO cohort and expectations about secondary endpoints in this population.

Hypothesis tests for other endpoints will not serve as the basis for inferential labeling claims; reported p-values will be based on nominal values not adjusted for multiple comparisons.

8.5 Observational Efficacy Assessment Analyses

Additional observational assessments of effectiveness will be evaluated including but not limited to between-group differences and within-group changes. Analyses will be based on evaluable data, except for night-time BP at 2 months where imputation will be used with the same method used for other 2 month endpoints.

- Reduction in average night-time ambulatory systolic/diastolic BP at 2, 6 and 12 months post procedure
- Reduction in average daytime & 24-hr ambulatory systolic BP at 6 and 12 months post procedure
- Reduction in average daytime & 24-hr ambulatory diastolic BP at 6 and 12 months post procedure

- Reduction in average office systolic BP at 6, 12, 24, 36, 48 & 60 months post procedure
- Reduction in average office diastolic BP at 6, 12, 24, 36, 48 & 60 months post procedure
- Reduction in average home systolic/diastolic BP at 1, 3, 4, 5, 6, and 12 months post procedure
- Blood pressure (systolic/diastolic daytime, nighttime, 24-hr ABP, home, and office) changes from baseline stratified by patients on/off antihypertensive medications and by # of medications
- Change in office systolic and diastolic BP from screening to 6, 12, 24, 36, 48 & 60 months post procedure
- Incidence of ambulatory systolic BP (daytime/24-hr/night-time) reductions of ≥5 mmHg, ≥10 mmHg, ≥15 mmHg, and ≥20 mmHg at 2, 6 and 12 months post procedure
- Percentage of subjects who are controlled in the absence of antihypertensive medication in each arm at 2, 6 and 12 months post procedure (daytime ABP <135/85 mmHg; night-time ABP < 120/70; 24-hr ABP< 130/80 mmHg; office BP <140/90 mmHg; office BP < 130/80 mmHg; home <135/85 mmHg; home <130/80 mmHg)
- Percentage of subjects who are controlled at 2, 6 and 12 months post procedure (daytime ABP <135/85 mmHg; night-time ABP < 120/70; 24-hr ABP< 130/80 mmHg; office BP <140/90 mmHg; office BP <130/80 mmHg; home <135/85 mmHg; home <130/80 mmHg) for home, office, and ambulatory BP.
- Time to first achieve blood pressure control post procedure (daytime ABP <135/85 mmHg; night-time ABP < 120/70; 24-hr ABP< 130/80 mmHg; office BP <140/90 mmHg; office BP < 130/80 mmHg; home <135/85 mmHg; home <130/80 mmHg) for home, office, and ambulatory BP.
- Visit-to-visit variability of BP excluding Baseline for visits at 2 months and beyond as calculated via the various methods outlined in publication by Hussein et al.[4]
- Change in office and ambulatory pulse pressure at 2, 6 and 12 months post procedure
- Change in office and ambulatory heart rate at 2, 6 and 12 months post procedure
- Antihypertensive medication burden (as defined in section 8.9.3) at 6 and 12 months post procedure
- Percentage of subjects requiring initiation of antihypertensive drug therapy between 2 and 6 months post procedure
- Percentage of subjects without any antihypertensive treatment at 6 and 12 months post procedure
- Percentage of subjects on antihypertensive drug therapy at any available timepoints post procedure
- Change in medication burden from screening to 6, 12, 24, 36, 48 & 60 months post procedure
- Comparison of clinic and remote ABP placement. This will be based on a repeated measures approach, incorporating all BP measures for subjects, with a fixed effect for type of collection (clinic vs. remote ABP).

All observational efficacy analyses for blood pressure, pulse pressure, and heart rate assessments will be run adjusting for medication burden (number of medications) via methods outlined in 8.9.3 in addition to the standard non-adjusted analyses.

Medication status for 2mo, 6mo, and 12mo visits will be based on medications taken on the date of the corresponding visit Ambulatory Blood Pressure start date (when available). If a valid ABP is not available for any timepoint, including visits where collection of ABP is not required, medication status will be based on medications taken on the date of the corresponding Office follow-up visit date.

8.6 Primary Safety Endpoint Analysis

The primary safety endpoint will be compared to a pre-specified performance goal of 9.8%. The estimated sample size of 128 treated subjects should provide 95% power for the performance goal if the population safety rate is approximately 3.0%.

Event frequency, rate (% of subjects), and exact 95% confidence intervals will be presented for each event type, and for the combined MAE composite for both the treatment arm, and the sham control arm. Frequency rates will be compared between treatment groups.

8.6.1 Primary Safety Endpoint

The primary safety endpoint is defined as a patient level composite of the incidence of the following Major Adverse Events (MAE);

The 30-day post randomization incidence of:

- All-cause mortality
- New onset (acute) end-stage renal disease (eGFR< 15 mL/min/m2 or need for renal replacement therapy)
- Significant embolic event resulting in end-organ damage (e.g., kidney/bowel infarct, lower extremity ulceration or gangrene, or doubling of serum creatinine)
- Renal artery perforation requiring an invasive intervention
- Renal artery dissection requiring an invasive intervention
- Major vascular complications (e.g., clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm) requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion (requiring more than 2 units of packed red blood cells within any 24-hr period during the first 7 days post randomization)
- Hospitalization for hypertensive or hypotensive crisis
- Hospitalization for major cardiovascular- or hemodynamic- related events (e.g. HF; MI; Stroke)
- New onset Stroke
- New onset Myocardial Infarction

And,

- The 6-month post randomization incidence of: New renal artery stenosis >70%, confirmed by CT or MR angiography.

The assessment of safety will be on CEC adjudication of Adverse Events for all components of the MAE definition, with the exception of renal artery stenosis, which is determined based on Imaging Corelab Assessment.

In addition, all safety events will be calculated for each study arm (treatment and control), assessed by the CEC and DSMB; and compared between and within arms (where applicable) for the duration of the study.

8.7 Additional Safety Assessment Analyses

Additional assessments of safety will be evaluated, including but not limited to:

- Incidence of post procedural pain (difference in average score on Pain Numeric Rating Scale between pre-procedure and hospital discharge score)
- Incidence of post procedural pain lasting > 2 days
- Incidence of severe post procedural pain defined as a score of ≥ 8 on the Visual Analog Scale (and assuming that baseline score was ≤ 4)
- Significant decline in renal function defined as ≥ 40% reduction in eGFR at 2, 6, & 12 months post procedure
- Change in mean eGFR at 2, 6, and 12 months post-procedure
- Change in mean plasma creatinine at 2, 6, and 12 months post-procedure

Kaplan-Meier analyses may be performed to examine the timing of incidence for events of interest.

8.8 Blinding Index

The effectiveness of blinding will be assessed at discharge, 2-months, 6-months and 12-months as follows:

- The numbers and proportions of subjects who guessed their treatment assignments correctly, incorrectly, and unknown, will be stratified by treatment group.
- The Blinding Index will be calculated according to the methods described in the Bang et al.[1] and James[2] publications.

8.9 Sub-Group Analyses & Exploratory Analyses

Additional, ad hoc exploratory analyses may also be conducted. These will be clearly labeled as exploratory and will include justification when reported.

8.9.1 Pre-Specified Subgroup Analyses

While no differences in results are expected for any of the defined subgroups, Primary and Secondary endpoint results by these subgroups will be examined.

The groupings for continuous variables (e.g. age) will use the median to split the data.

Sex differences will be evaluated following the FDA guidance document "Evaluation of Sex-Specific Data in Medical Device Clinical Studies" released August 22, 2014.

Pre-specified evaluations of efficacy will be evaluated in specific subgroups including but not limited to:

- Sex
- Race (Black versus non-black)
- Age
- Baseline ambulatory daytime systolic BP
- Baseline office systolic BP
- Baseline home systolic BP
- Average baseline 24 hour ABP heart rate (above and below median)
- eGFR (<60 vs. ≥ 60)
- Geography
- Abdominal obesity split for male >102cm and ≤102cm; and for female >88cm and ≤88cm
- Number of ablations performed (Treatment Group only)
- Presence of untreated accessory arteries (Treatment Group only)
- Balloon size (Treatment Group only)
- Pre/post COVID-19 enrollment (i.e. 95 subjects enrolled prior to the enrollment stoppage due to COVID-19 vs. those enrolled later)
- In addition to the evaluation of efficacy for these groups, patient baseline characteristics will be compared for the pre/post COVID-19 enrollment groups.

8.9.2 Pre-Specified Multivariable Analysis

A multiple linear regression analysis on the per-protocol population to assess the predictive variables of the changes in daytime ambulatory systolic blood pressure will be conducted. For the analysis, the dependent variable will be the change in daytime SBP from baseline to 2-months, and the independent variables will include:

- Group (Denervation =1, sham = 0)
- Sex
- Race (Black versus non-black)
- Age
- Baseline ambulatory daytime systolic BP
- Baseline office systolic BP
- Baseline home systolic BP
- Average baseline 24 hour ABP heart rate (above and below median
- eGFR <60
- Geography
- Abdominal obesity split for male >102cm and ≤102cm; and for female >88cm and ≤88cm

8.9.3 Other Pre-Specified Analyses for Publication

Additional sub-group analyses based on COVID vaccination status and positive cases may be conducted. Methods will follow those for other subgroup analyses

A pooled analysis with the subset of RADIANCE-HTN SOLO patients matching RADIANCE-II inclusion and exclusion criteria will be conducted. Analyses will be based on linear mixed effects model for change in BP, adjusted for baseline, treatment group as fixed effects and study as a random effect.

8.9.4 Sensitivity Analyses for impact of medication changes

Blood pressure medication use during the trial, including changes to medication, may affect the blood pressure endpoints. While attempting to adjust for data collected post-randomization (e.g. medication use) is difficult to interpret as it can induce a bias of an unknown direction and magnitude, the following analyses will be performed to help assess the impact of medications.

1) The randomized treatment arms will be compared for the proportion of subjects with any change in blood pressure medication (number, type, or dosage of medications) between baseline and the 2-month endpoint assessment.
2) Overall and by randomized treatment arm, the baseline covariates and 1-month BP measurements will be compared between patients with and without any change in blood pressure medication (number, type, or dosage of medications) between baseline and the 2-month endpoint assessment.
3) Drug burden will be calculated in the following ways:
    - Number of medications: each medication will be given a score of 1 and sum of these will be counted for a given visit.
    - Actual dose will be divided by the maximum dose for each agent, and the values for each agent will be added for a given visit (Wan et al.).[5]
    - Defined daily dose as established by the World Health Organization for each agent will be added together for a giving visit (WHO reference).[6]

For each of the drug burden indices the following will be performed:

- The score for both treatment and sham groups will be calculated for the following visits: V0 (Screening), V3 (2-month visit), V4 (3-month visit), V5 (4-month visit), V6 (5-month visit), V7 (6-month visit), and V8 (12-month visit). Both absolute values and change from V0 for each medication burden index (mean and medians) will be compared between groups.
- The absolute values of each medication burden score (mean and medians) will be compared between groups considering office and/or ambulatory blood pressures.
- A comparison will be made for each treatment group in the office BP (systolic and diastolic) and the distribution of patients on 0, 1, or 2 medications at Screening (V0) vs. 6-months (V7), and Screening vs. 12-months (V8).
- For each subject, a comparison of body weight will be done between baseline and 6-months, and between baseline and 12-month.

9. DURABILITY ANALYSIS

Analyses of the durability of denervation will be performed. This will consist of presentation of summary statistics at baseline, 6 months, and 12 months for medication usage, and maximum likelihood based on linear repeated measures models for blood pressure (home, office, and ambulatory) and medication burden[5,6] over time. This will also be performed for office from screening blood pressure and medication burden (instead of baseline) through 6 and 12 months.

Focus will be on the outcomes over time for subjects treated initially with denervation. Additional analyses will be performed for subjects initially treated as control, up to the time of crossover. In addition, we will look at cross-over subjects after the time of crossover to assess durability of denervation.

Time from baseline will be treated as a categorical variable. A compound-symmetric covariance structure will be used to account for within subject correlation.

All available BP measurements and medication data will be used without imputation of missing data. Least-square mean estimates and nominal 95% confidence intervals will be reported.

The durability analysis will be performed separately for RADIANCE II, RADIANCE HTN SOLO Cohort, and the RADIANCE HTN TRIO Cohort.

10. RADIANCE STUDIES POOLED SAFETY ANALYSES

10.1 Overall Summary

The overall purpose of the pooled safety analysis is to characterize rare events and provide an overall summary of the totality of the safety data. Studies/cohorts will include the RADIANCE II subjects, RADIANCE HTN SOLO Cohort, the RADIANCE HTN TRIO Cohort. This will be referred to as the Pooled Safety Population.

The primary focus will be on characterizing the Pooled Safety Population for treated and sham subjects from the RADIANCE trials through 12 months/up until crossover for sham subjects. Additional analyses will be supportive in nature and may include longer term data and data from the REQUIRE and ACHIEVE study subjects.

10.2 Time points

Key time points for analysis will include 30 days, 6 months, 12 months, and additional available longer-term follow-up through 5 years.

10.3 Planned analyses

The primary focus will be on treated subjects. Additionally, analyses will be performed separately for treated and control subjects, as appropriate.

Kaplan-Meier analysis along with along with nominal 95% confidence intervals will be provided.

10.4 Analysis Populations

The primary analysis population will consist of subjects treated with the investigational device. For analyses including control subjects, the control group analysis population will consist of all subjects who underwent a sham procedure.

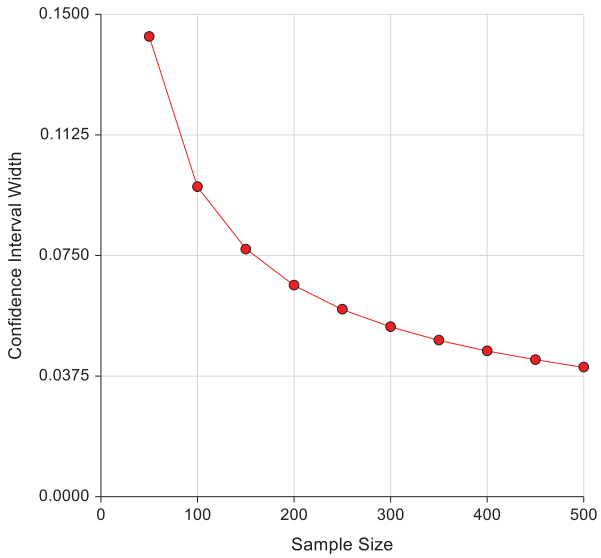
10.5 Sample Size Assessment

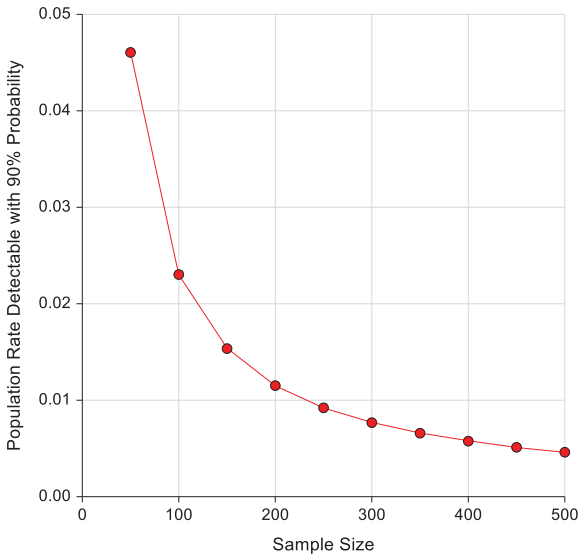
The expected sample size for the Pooled Safety Population is expected to provide a reasonable amount of data to characterize rare events and provide an overall summary of the totality of the safety data. In particular, safety data is expected for more than 300 treated subjects and 200 control subjects through 30 days, and 250 treated subjects and 170 control subjects through 12 months.

The figures below help quantify the degree of statistical information this will provide. The first provides the width of a 95% confidence interval for an observed event rate of 5% (the value of 5% was arbitrarily chosen for the purposes of illustration), and the second figure provides the background population rate that would be detectable with 90% probability as a function of sample size. The sample sizes provided range from the upper end of the treated subjects (300 subjects) down to 50 (corresponding to later time periods, e.g. subjects past 2 years).

These show that the confidence interval with is expected to be less than 10% for most time points based on the number of expected subjects and that rare events are highly likely to be observed for population event rates lower than 1% for early time points (30 days, 12 months) and rates lower than 5% for late time points (2+ years).

10.5.1 Summary of Statistical Measures for Safety versus Sample Size





10.6 Pooled Safety Endpoints

The following outcomes will be examined for the Pooled Safety Analysis:

- Combined MAE rate
- Each component of MAE:
  - All-cause mortality
  - New onset (acute) end-stage renal disease (eGFR< 15 mL/min/m2 or need for renal replacement therapy)
  - Significant embolic event resulting in end-organ damage (e.g., kidney/bowel infarct, lower extremity ulceration or gangrene, or doubling of serum creatinine)

- Renal artery perforation requiring an invasive intervention
- Renal artery dissection requiring an invasive intervention
- Major vascular complications (e.g., clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm) requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion (requiring more than 2 units of packed red blood cells within any 24-hr period during the first 7 days post randomization)
- Hospitalization for hypertensive or hypotensive crisis
- Hospitalization for major cardiovascular- or hemodynamic- related events (e.g. HF; MI; Stroke)
- New onset Stroke
- New onset Myocardial Infarction
- New renal artery stenosis >70%, confirmed by CT or MR angiography

Subgroup analyses for the pooled safety analysis will be performed based on subgroups defined by the following baseline characteristics:

- Renal artery diameter (subjects with 1 or more renal arteries treated with a balloon size ≤4.2 mm vs. other subjects)

Subgroup analyses will be exploratory in nature. The proportion of subjects with events will be compared based on regression models. A p-value of <0.15 for a subgroup effect (a main effect for analyses looking at the treated subjects, treatment by subgroup interactions for analyses comparing treated and control subjects) will be used as a threshold for additional exploratory analysis to understand and quantify result by subgroups.

Baseline characteristics will be assessed for their association with the combined MAE rate. Any statistically significant associations based on a p-value of 0.05 from a log-rank test will be identified. Any such identified baseline characteristics will then be compared between study groups to assess potential differences between groups for such characteristics.

11. DATA STRUCTURE AND HANDLING

11.1 Missing Data

See section 8.3.1 and 8.3.2 above.

11.2 Pooling of Data Across Trial Sites

Poolability of results across trial sites will be assessed by comparing treatment/control differences in the primary effectiveness endpoint across sites. Sites with 5 or fewer subjects will be pooled into one meta-site to facilitate analysis. The effect of treatment across sites will be tested in a linear regression analysis. Specifically, the following equation will be used for the primary efficacy endpoint:

$$Y = \beta_0 + \beta_{txt}*X_{trt} + \beta_{center}*X_{center} + \beta_{txt*center}*X_{trt}*X_{center} + \beta_{bl}*X_{bl}$$

Where

- Y = the reduction in ambulatory systolic BP from baseline to 2 months post-procedure
- β_{txt} = the regression coefficient associated with the treatment term

- X_{trt} = a indicator variable for treatment group, with a value of 1 for the treatment group and 0 for the control group
- B_{center} = the regression coefficient associated with the investigational center
- X_{center} = a classification factor for investigational center (e.g. used with a CLASS statement in SAS)
- $\beta_{txt*center}$ = the regression coefficient associated with the treatment by center interaction term
- B_{bl} = the regression coefficient associated with the baseline ABP
- X_{bl} = the baseline ABP

Significance will be tested at the 0.15 level for $\beta_{txt*center}$. A significant finding would be further investigated to try to understand the cause of the interaction, and additionally, a model with a random site effect, in addition to fixed effect for treatment and baseline ABP, will be fit.

12. REFERENCES

1. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials 2004; 25:143-56.
2. James KE, Bloch DA, Lee KK, Kraemer HC, Fuller RK. An index for assessing blindness in a multicentre clinical trial: Disulfiram for alcohol cessation – a VA cooperative study. Stat Med. 1996;15:1421-34.
3. Rubin, D. B. (1976). "Inference and Missing Data." Biometrika 63:581-592.
4. Hussein et al. Visit-to-Visit Variability of Systolic Blood Pressure and Cardiovascular Disease. Curr Hypertens Rep. 2015 Mar;17(3):14.
5. Wan S-H, Hart M, Hajjar I. A novel measurement index for antihypertensive medication burden and its use. Hypertens (Dallas, Tex 1979) 2009; 54:e135-6.
6. World Health Organization Collaborating Centre for Drug Statistics Methodology:https://www.whocc.no/ddd/definition_and_general_considera/ (accessed July 25, 2018).