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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 HTN" Study.

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 HTN Study protocol version A, dated December 11, 2015. Any further changes to the protocol or eCRF may necessitate updates to the SAP. This revision (version A) of the SAP was finalized before unblinding of any outcome data from the RADIANCE-HTN Clinical Study.

3. APPLICABLE DOCUMENTS

Document Number	Title
CLN-0001	CLN-0777 ReCor RADIANCE HTN Study protocol
NAMSA STATSOP-002	Statistics Standard Operating Procedure – Statistical Analysis Plan

4. SOFTWARE

All tables, listings and figures will be produced using SAS Version 9.3 (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-HTN study is to demonstrate the efficacy and verify the safety of the Paradise System in two distinct populations of hypertensive subjects. Prior to randomization, subjects will be hypertensive in the absence of hypertension medication or despite the presence of a stabilized, single pill, triple, fixed dose antihypertensive medication regimen.

6. TRIAL DESIGN

RADIANCE-HTN is a randomized, double-blind, sham controlled, 2-cohort study designed to demonstrate efficacy and document the safety of the Paradise Renal Denervation System in two distinct populations of hypertensive subjects.

6.1 Cohorts

Two study cohorts will be evaluated. Subjects with essential hypertension controlled on 1 or 2 antihypertensive medications or uncontrolled on 0-2 antihypertensive medications will be included in the RADIANCE Solo cohort while subjects with treatment resistant hypertension on a minimum of 3 antihypertensive medications will be included in the RADIANCE Trio cohort.

The two cohorts will be analyzed independently for all endpoints. Analysis of each cohort's data can be conducted when enrollment and sufficient follow-up completes in a specific cohort.

6.2 Randomization

Separate randomization schedules will be generated for the Solo and Trio Cohorts. A 1:1 randomization scheme will be used in both cohorts 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.

6.3 Blinding

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

6.4 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 separately for each cohort at the point of the Primary Efficacy Endpoint. Calculations are based on evaluating the treatment versus control groups for 1) the RADIANCE Solo and 2) RADIANCE Trio cohorts) independently.

Statistical analyses will be performed separately for the RADIANCE Solo and RADIANCE Trio cohorts, each at a two-sided 0.05 alpha level as there is independent interest in conclusions for each cohort separately. 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 follow-up. Based on a two-sample t-test, for an assumed mean±standard deviation difference of 6±12 mmHg, a planned evaluable sample size of 128 subjects per cohort will provide 80% power. These calculations can be confirmed with the following SAS System (version 9.3) code:

```
proc power;
twosamplemeans test=diff
meandiff = 6
stddev = 12
alpha = 0.05
power = 0.80
ntotal = . ;
run;
```

To account for the loss of power due to missing data, an approximate 10% inflation is used so the total randomized per cohort is planned at 146 subjects, or 292 total.

Based on enrollment challenges due to the COVID-19 pandemic and a blinded evaluation of the extent of missing data, enrollment was stopped on May 8, 2020 for the RADIANCE Trio cohort since the expected evaluable total exceeded the 128 originally planned sample size, consistent with FDA guidance "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry" released June 2020.

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 where 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 9.13.2 Clinical Protocol) necessitating the re-start (SOLO Cohort) or addition (TRIO Cohort) of anti-hypertensive medication prior to the 2-month primary endpoint. The mITT population for the SOLO Cohort is concordant with that defined in the SPYRAL HTN-OFF MED Clinical Study [1].

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
- Documented secondary hypertension (Trio cohort)
- Failure to obtain 2 month follow-up ABP recording
- Subjects necessitating the re-start (SOLO cohort) or addition (TRIO cohort) of 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 PP and AT populations.

Note that the terms for subject classification defined in the protocol ("intent", "attempt", and "treatment" subjects, Section 8.3) 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 Effectiveness 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 missing the reduction in blood pressure value, a value of zero will be used for the reduction in blood pressure in the analysis.

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. This mirrors the method reported in SPYRAL HTN-OFF MED publication [2].

This ANCOVA model assumes a normal distribution of residuals. To handle the case where an assumption of normality may be in question, we will perform additional analyses of the primary effectiveness endpoint to examine the robustness of the finding with respect to this assumption. This analysis will be based on ranking the observations 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.

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

The statistical analysis of the secondary efficacy endpoints will follow the methodology of the primary Efficacy Endpoint but will be based on:

- Reduction in average 24-hr/night-time ambulatory systolic BP at 2 months post procedure (2 assessments).
  - Reduction = [(average 2 month ambulatory systolic BP) - (average baseline ambulatory systolic BP)] for both 24-hr and night-time.
- Reduction in average daytime/24-hr/night-time ambulatory diastolic BP at 2 months post procedure (3 assessments).
  - Reduction = [(average 2 month ambulatory diastolic BP) - (average baseline ambulatory diastolic BP)] for 24-hr and night-time.

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:

1. Reduction in average 24 hour ambulatory systolic BP at 2 months
2. Reduction in average 24 hour ambulatory diastolic BP at 2 months
3. Reduction in average night-time ambulatory systolic BP at 2 months
4. Reduction in average night-time ambulatory diastolic BP at 2 months

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 Safety Assessments

The assessment of safety will be based primarily on the frequency of serious adverse device effects (SADEs) serious adverse events (SAEs), adverse device effects (ADEs), adverse events (AEs) and laboratory abnormalities classified by Investigators as related to the renal denervation and confirmed by the DSMB. Occurrence and frequency of SADEs and ADEs and AE(s) and SAE(s) will be summarized by treatment group at baseline, last visit (duration of the study) and by changes from baseline to last visit for laboratory values. Event frequency, rate (% of subjects), and exact 95% confidence intervals will be presented for each event type by treatment group.

Specific events of interest will be summarized by treatment group for their incidence, based on the percentage of subjects experiencing events. These include the following:

- All-cause mortality
- Hypertensive emergency resulting in hospitalization
- Hypotensive emergency resulting in hospitalization
- Hospitalization for heart failure
- Stroke, transient ischemic attack, cerebrovascular accident
- Acute myocardial infarction (STEMI/non-STEMI)

- Any coronary revascularization
- End stage renal disease, the need for permanent renal replacement therapy (i.e. the need for dialysis); doubling of plasma creatinine
- Any renal artery complication requiring intervention (e.g. dissection; perforation)
- Major access site complications requiring intervention
- Significant embolic events resulting in end organ damage
- Procedure-related pain lasting for > 2 days
- Acute renal injury, defined as:
- Increase in plasma/serum creatinine by ≥ 0.3 mg/dl (≥26.5 µmol/l) within 48hrs of the procedure or,
- Increase in serum/plasma creatinine to ≥1.5 times baseline known to have occurred during 7 days post procedure or
- Urine volume <0.5 ml/kg/h for 6 hours
- Significant (>50%) and severe (>75%) new onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA
- Need for renal artery angioplasty or stenting

Kaplan-Meier analyses may be performed to examine the timing of incidence for events of interest. Formal statistical comparisons may be made with log-rank tests, with p-values less than 0.05 considered statistically significant. Kaplan-Meier estimates will also be produced for the following events at the specified time points:

<u>1 month post procedure event rates:</u>

- Any renal artery complication requiring intervention (e.g. dissection; perforation)
- Major access site complications requiring intervention
- Significant embolic events resulting in end organ damage
- Procedure-related pain lasting for > 2 days
- Acute renal failure, defined as:
    - Increase in plasma/serum creatinine ≥ 0.3 mg/dl (≥26.5 µmol/l) within 48hrs of the procedure or,
    - Increase in serum/plasma creatinine to ≥1.5 times baseline known to have occurred during 7 days post procedure or
    - Urine volume <0.5 ml/kg/h for 6 hours

<u>6, 24 & 36 months post procedure event rates:</u>

- Significant (>50%) and severe (>75%) new onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA
- Need for renal artery angioplasty or stenting

12 months post procedure event rates:

- Significant (>50%) and severe (> 75%) new onset renal stenosis as diagnosed by study-defined renal CTA/MRA
- Need for renal artery angioplasty or stenting

The following observational assessments will also be described with descriptive statistics (counts and percentages, or mean / standard deviation, as appropriate):

- Level of post-procedural pain as determined by the use of a Visual Analog Scale
- Incidence of severe procedural pain defined as a score of ≥ 8 on the Visual Analog Scale
- Incidence of new onset orthostatic hypotension post procedure
- Change (reductions) from baseline in mean eGFR at 2, 6, & 12 months post-procedure
- Change (increases) from baseline in mean plasma creatinine at 2, 6 & 12 months post-procedure

Safety MAE Rate

In addition to the reporting of all safety events, a composite Major Adverse Event (MAE) Rate will be determined including the events listed below. 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.

- 30-day events included in MAE
  - Death from any cause
  - Renal failure (eGFR <15mL/min/m^2 or need for renal replacement therapy or doubling of serum creatinine
  - An embolic event resulting in end-organ damage
  - Renal artery, or other major vascular complications requiring intervention
  - Hospitalization for hypertensive crisis
- 6-month events included in MAE
  - New onset renal artery stenosis of more than 70%

8.6 Blinding Index

The effectiveness of blinding will be assessed at discharge, 2-months, and 6-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 method described in Bang et al. [2]

8.7 Observational Assessments

- Reduction in average office systolic/diastolic BP at 2, 6 and 12 months post procedure (6 assessments)

- Reduction = [(average follow-up office BP) - (average baseline office BP)] for each BP type and at each time point.

- Reduction in average daytime/24-hr/night-time ambulatory systolic BP at 6 and 12 months post procedure (6 assessments)
  - Reduction = [(average follow-up ambulatory systolic BP) - (average baseline ambulatory systolic BP)] for each time of day and at each time point.
- Reduction in average daytime/24-hr/night-time ambulatory diastolic BP at 6 and 12 months post procedure (6 assessments)
  - Reduction = [(average follow-up ambulatory diastolic BP) - (average baseline ambulatory diastolic BP)] for each time of day and at each time point.
- Reduction in average home systolic/diastolic BP at 2, 3, 4, 5 and 6 months post procedure (10 assessments)
  - Reduction = [(average follow-up home BP) - (average baseline home BP)] for each BP type and at each time point.
- Incidence of ambulatory systolic BP (daytime/24-hr/night-time) reductions of ≥5 mmHg, ≥10 mmHg, and ≥15 mm Hg at 2, 6 and 12 months post procedure (27 assessments)
- Percentage of subjects who are controlled in the absence of any changes in hypertensive medication (any change in the number, type, or dosage of medications) in each arm at 2, 6 and 12 months post procedure. The cutoffs of "controlled" blood pressure are as follows: daytime ABP <135/85 mmHg; night-time ABP < 120/70; 24-hr ABP< 130/80 mmHg; office BP <140/90 mmHg) (3 time points by 4 cutoffs, for a total of 12 assessments)
- Percentage of subjects who are controlled including any changes in hypertensive medication (any change in the number, type, or dosage of medications) in each arm at 2, 6 and 12 months post procedure. The cutoffs of "controlled" blood pressure are as follows: daytime ABP <135/85 mmHg; night-time ABP < 120/70; 24-hr ABP< 130/80 mmHg; office BP <140/90 mmHg) (3 time points by 4 cutoffs, for a total of 12 assessments)
- Change in office and ambulatory pulse pressure at 2, 6 and 12 months post procedure (6 assessments)
  - Change = [(follow-up pulse pressure) - (baseline pulse pressure)]
- Change in office and ambulatory heart rate at 2, 6 and 12 months post procedure (6 assessments)
  - Change = [(follow-up heart rate) - (baseline heart rate)]
- Antihypertensive treatment score (antihypertensive load [3]) (number of antihypertensive drugs, doses, classes) at 6 and 12 months post procedure (2 assessments)
  - Change = [(follow-up Antihypertensive treatment score) - (baseline Antihypertensive treatment score)]
- Percentage of subjects requiring initiation of additional antihypertensive drug therapy between 2 and 6 months post procedure (2 assessments)

- "additional antihypertensive drug therapy" is defined as any increase in antihypertensive treatment score.

- Percentage of subjects without any antihypertensive treatment at 6 and 12 months post procedure in the RADIANCE Solo cohort (2 assessments)
  - "without any antihypertensive treatment" is defined as an antihypertensive treatment score of 0.
- Compliance assessed by urine drug level determinations
- Change in plasma biomarkers at 2 and 6 months post procedure (Solo cohort only, optional) (multiple assessments)
- Percentage of patients in whom it is possible to deliver complete ablation profile (as determined by individual anatomy)

8.8 Exploratory Analyses

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

8.8.1 Subset 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.

Sub-group analyses by demographic factors such as age, race, and sex will be conducted. The groupings for continuous variables (e.g. age) will be 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.

Additional exploratory subgroup analyses that will be performed to determine potential interactions include the following:

- Geography: US vs EU/UK
- Baseline (V1) daytime ambulatory systolic blood pressure
- Baseline (V1) office systolic blood pressure
- Abdominal obesity split for male >102cm and ≤102cm; and for female >88cm and ≤88cm
- Total number of bilateral emissions (4,5,6,>6)

8.8.2 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)
- Age
- Sex
- White ethnicity

- Baseline daytime systolic blood pressure
- Baseline nighttime systolic blood pressure
- Baseline diastolic blood pressures
- Average baseline ABP heart rate
- BMI
- eGFR
- Number of medications at screening
- Total number of ablations
- Presence of accessory arteries
- Average vessel diameter

8.8.3 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.

9. DATA STRUCTURE AND HANDLING

9.1 Missing Data

See section 8.3.2 above.

9.2 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 effectiveness 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)

- βtxt*center = the regression coefficient associated with the treatment by center interaction term
- Bbl = the regression coefficient associated with the baseline ABP
- Xbl = 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.

10. REFERENCES

1 Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, *et al.* Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017; 390:2160-2170.

2 Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004; 25:143-56.

3 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.