CLINICAL STUDY PROTOCOL

The "RADIANCE II" Pivotal Study
A Study of the ReCor Medical Paradise System in Stage II Hypertension

Protocol Number: CLN 0841

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Revision History

Revision Number	Release Date	Description
A	June 26, 2018	Initial Release
B	March 2, 2020	• Addition of QoL data collection, including at minimum, EQ-5D-5L questionnaire, and added collection of QoL at Screening; • Minor wording clarification to distinguish inclusion criterion assessed at Screening and which are assessed prior to randomization; • Updates to exclusion criteria for planned pregnancy to specify planned pregnancy within 12 months of procedure; • Updated blinding to be maintained through 12mos post-procedure; • Addition of Home Blood Pressure Measurements at 12mos; • Addition of 4 & 5 Year follow-up visits; • Additional Observational Efficacy endpoint to account for evaluation of anti-hypertensive drug therapy at any timepoint; • Minor wording clarification of timeframe for MAE components of Primary Safety endpoint; • Addition of 3.5mm balloon and update to renal artery diameter size eligible for treatment and additional treatment strategy figures; • Update of requirement for 12-month follow-up imaging to apply to Treated Subjects only; • Clarification of safety escape criteria and medication escalation requirements; • Update to assessment for AE relationship to study device or procedure; • Addition of cross-over visit schedule; • Addition of Cross-Over data collection (Pain Perception Questionnaire, 12-Lead ECG, Urine for drug Metabolite and Home BP Diary); • Update of company contact information and Corelab information; • Update the radiation exposure risk to include the potential teratogenic damage, if pregnant; • Correction of typographical errors and minor clarifications.
C	April 1, 2020	• Final Clarification of wording regarding High BP and Low BP Action.
D	July 8, 2021	• Addition of COVID-19 related changes to assessments to allow for the remote conduct of follow-up visits due to COVID-19 public health emergency; • Addition of safety assessments of AEs due to COVID-19; • Addition of new SOLO cohort study results; • Clarifications to guide catheters and guide wires; • Updates to Minimization of risk to clarify how safety oversight will continue during COVID-19 public health emergency; • Updated Re-consent section to allow patients withdrawn during screening due to COVID-19 enrollment suspension, may be approached for re-consent, upon sponsor approval; • Added COVID-19 public health emergency as a reason for study withdrawal;

Revision Number	Release Date	Description
		• Updated the Visit Schedules to notate which follow-up assessments may be conducted remotely due to COVID-19 restrictions; • Addition of Visit Schedule notations to clarify that if a follow-up the CRA/MRA cannot be performed per visit window, due to COVID-19 restrictions, imaging may be conducted up to 90 days post the 6- and 12-month follow-up visits; • Updated to clarify that the 24-hr ABPMs may be initiated remotely; • Updated to allow for use of Home BP diary review will be used to determine need for clinical intervention or medication escalation, in the event a visit cannot be conducted in-person due to COVID-19; • Added COVID-19 Adverse Event Definitions; • Added section describing how COVID-19 protocol deviations shall be evaluated and reported; • Clarifications to monitoring procedures to allow for remote monitoring at sites; • Specified sponsor local representatives in EU and UK; • Updated to clarify that anti-hypertensive drug adherence testing needs to coincide with each 24hr-ABP measurement and specified timing of urine collection in relation to initiation of ABPM; • Updated to include the urine drug metabolite collection at cross-over baseline and cross-over 2M FU visits; • Updated to clarify that if elevated hypertension is sustained over 3 consecutive days of Home BP recordings, then medication escalation is recommended; • Updated a new higher quality image of Generator and Accessories; • Updated to clarify that any data collected remotely will be documented in EDC; • Updated to clarify circumstances where ABP measurement should be repeated and to contact the sponsor to ensure a repeat ABP is appropriate; • Added additional details of imaging core lab for imaging uploads, database and address; • Correction of typographical errors and minor clarifications.

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1. Study Summary

Introduction	The ReCor Medical Paradise® Renal Denervation System (Paradise System) is a catheter-based system that delivers ultrasound energy to thermally ablate and disrupt the renal efferent and afferent sympathetic nerves while sparing the renal arterial wall. The goal of renal nerve ablation is to achieve a reduction in sympathetic over-activity with the resultant effect of reducing systemic arterial blood pressure (BP), and mitigating resultant end organ damage.
Study Objective	The objective of the RADIANCE II Pivotal study is to demonstrate the effectiveness and safety of the Paradise System in subjects with Stage 2 hypertension on 0-2 anti-hypertensive medications of different classes at the time of consent. Prior to randomization, subjects will be hypertensive in the absence of hypertension medication.
Study 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.
Patient Population	Subjects with Stage 2[1] hypertension on no more than two (2) anti-hypertensive medications of different classes at the time of consent will be included in RADIANCE II. Subjects with no history of treatment with anti-hypertensive medications will be excluded. Subjects with hypertension, defined as an average seated office BP ≥ 140/90 mmHg and < 180/120 mmHg at Screening (V0), currently taking anti-hypertensive medication will undergo a 4-week washout period of drug discontinuation. Drug discontinuation will occur in accordance with accepted, institutional guidelines for the subjects' current medication. Subjects not taking any anti-hypertensive medication will undergo a 4-week run-in period. After 4 weeks of drug discontinuation or run-in, all subjects will undergo a second office BP check. Assuming that the subject has not met the safety escape criteria during the washout/run-in period, they will undergo a 24-hr ambulatory BP (ABP) measurement. Subjects whose daytime ABP remains ≥ 135/85 mmHg and <170/105 mmHg, require a baseline renal Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) to rule out renal abnormalities, renal artery pathology and/or significant renal artery stenosis, and to confirm anatomical eligibility if a cross-sectional imaging study (either CTA or MRA) is not already available that has been performed within one year prior to consent. Subjects with suitable renal artery anatomy on CTA/MRA will undergo a renal angiogram procedure. Subjects whose renal anatomy is re-confirmed as suitable will then be randomized to treatment ("renal denervation") or control ("sham").* **For those subjects randomized to control, the renal angiogram will be considered the sham procedure*
Follow-Up Schedule Post Procedure	The Primary Efficacy endpoint will be collected at 2 months post procedure; however all subjects will be followed for a minimum of 60 months post procedure. Follow-up (FU) visits will occur at 1, 2, 3, 4, 5, 6, 12, 24, 36, 48 & 60-months post procedure.

[1] Whelton et al., 2017 High Blood Pressure Clinical Practice guidelines. *Hypertension*

	Urine testing for medication adherence will occur at baseline (post washout/run-in), 2, 6, and 12 months FU. The date of collection of the urine for adherence testing will coincide with the date of initiation of the ABP measurement but not to exceed 24 hours after initiation. Quality of Life data will be collected using, at a minimum, the EQ-5D-5L validated questionnaire at Screening, Baseline, 2, 6- and 12-months FU. Patient preference data will be collected throughout the study via approved social or other media or more traditional quantitative or qualitative methods. All subjects will be provided with a Home BP monitor at the initiation of the drug washout/run-in period and asked to measure their home BP for the 7 consecutive days prior to the Baseline (V1), 1, 2, 3, 4, 5, 6 & 12-month FUs. All subjects will have seated office BP measurements taken at each clinic FU and 24-hr ABP measurements will be taken at 2, 6- and 12-months post procedure. A FU renal CTA or MRA will be performed at 6 months after the procedure in all subjects. An additional FU renal CTA or MRA will be performed at 12-months after the procedure only in subjects randomized to Treatment. Additional CTA/MRA imaging may be required at any time point if clinically indicated (e.g. increase in blood pressure, consistent with the protocol defined definition of 'High BP Criteria") or based on the required imaging study results (e.g. a change in the minimal lumen diameter along the renal artery ≥0.2mm).
Blood Pressure Measurements	To limit variability in BP measurements, scheduled in-clinic visits will occur in the morning (preferably between 08:00 and 10:00am). Up to and including the 12 month FU visit, subjects should bring any study-defined antihypertensive medications with them on the day of the FU. Investigational sites should contact the subject before the scheduled visit to remind them. Office BP measurements will be recorded and, when applicable, ABP device set up will be completed, prior to subjects being observed taking their antihypertensive medication(s). ABP measurements may be initiated remotely, if needed. Reference protocol section 9.3.3 for 24-hr ABP Measurement guidelines. Average Office BP will be measured at Screening, Baseline, 1, 2, 3, 4, 5, 6, 12, 24, 36, 48 & 60 month FU. Office BP at Discharge visit is optional. Average Home BP will be recorded for the 7 consecutive days immediately prior to baseline, 1, 2, 3, 4, 5, 6 and 12 month clinic FUs. Reference protocol sections 9.1 and 9.2 for Home Blood Pressure guidelines. Average values will be calculated according to the Statistical Analysis Plan. Where appropriate, average Home BP values are used to help determine the need for hypertension medication escalation (see below). Average Home BP recorded prior to the baseline visit will be used in the determination of any unacceptable risk to subjects from severely elevated BP occurring during the washout/run-in period. Average Home BP ≥170 mmHg systolic or ≥ 105 mmHg diastolic at Baseline, associated with clinical events considered to be related to persistent or elevated hypertension and verified by any of the following additional BP values will result in the subject being excluded (Safety Escape Criteria): • Average Office BP ≥ 180 mmHg systolic or ≥ 120 mmHg diastolic. • Daytime ABP ≥ 170 mmHg systolic or ≥ 105 mmHg diastolic
Randomization	A 2:1 randomization scheme will be used to assign subjects to treatment (renal denervation) or 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.
Blinding	The subjects and all study personnel taking FU blood pressure measurements will be blinded to the randomization. Subjects will complete a blinding assessment[2] prior to hospital discharge, at 2, 6 & 12 months FU. All ABP measurements will be collected via a core lab.
Changes in Anti-Hypertensive Medication	For the period of washout/run-in prior to the procedure, through to the 2-month Primary Efficacy endpoint visit, changes in medication outside the requirements of the study protocol may not occur other than: • As required to facilitate anti-hypertensive drug washout per standard Institutional guidelines • In the incidence of BP emergency associated with clinical events believed to be related to persistent or elevated hypertension • In the incidence of a clinical event in which a change in medication becomes medically necessary **Changes in Anti-Hypertensive Medication (Between 2- and 6-month FU)** Subjects are required to remain free of antihypertensive medication through to the 2-month Primary Efficacy endpoint visit unless necessitated as described above. Following the 2-month Primary Efficacy endpoint visit, all subjects will remain blinded through the 12-month visit. Introduction of antihypertensive therapy will occur as needed to achieve BP control following the completion of the 2-month FU Visit (including ABP). If the average Home BP is <135/85 mmHg, no action is required. **Between the 2- and 6-month FU visits, a pre-defined protocol for escalation of anti-hypertensive medication is required for subjects whose BP is not controlled.** At each FU visit between 2- and 6-months, BP control must be evaluated. If control is not achieved at any follow-up visit during this period, anti-hypertensive medication must be started or escalated to the next step sequentially, in the order indicated below, unless otherwise medically indicated. If the escalation is not followed, the site will be requested to provide supporting justification. • Medication escalation will start at the FU visit where a sustained elevation (≥135 mmHg systolic OR ≥85 mmHg diastolic) in average Home BP is recorded and confirmed by an average Office BP ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic. If a visit cannot be completed in-office due to the COVID-19 public health emergency, the Home BP Diary will be used to determine medication escalation. If elevated hypertension is sustained over 3 consecutive days, then medication escalation is recommended.

[2] Bang H, Ni L & Davis CE, Assessment of Blinding in Clinical Trials. 2004. Controlled Clinical Trials 25: 143-156

	• Drugs will be added sequentially at each monthly FU visit in the event BP remains uncontrolled. If medication escalation steps are not followed in order, justification must be provided. • Medication escalation will be at the discretion of the Investigator if only average Home BP or only average Office BP meets the criteria above. • **Step 1**- Add mid-dose long acting dihydropyridine calcium channel blocker (CCB) (preferentially Amlodipine 5 mg) • **Step 2**- Add full dose of long acting angiotensin receptor blocker (ARB) (preferentially Valsartan 160-320 mg; or Olmesartan 20-40mg) or Angiotensin Converting Enzyme inhibitor (ACEi; preferentially Ramipril 10-20mg or Lisinopril 20-40 mg) • **Step 3**- Add low dose of Hydrochlorothiazide (HCTZ; 12.5 mg) • **Step 4**- Increase dose of HCTZ (25 mg) • **Step 5**- Increase long acting dihydropyridine CCB to full dose (e.g. Amlodipine 10 mg) *Note: All recommended doses are once daily* Following the 6-month FU, subjects may have their medications modified per physician's discretion.
Medication changes due to High BP or Low BP (inclusive of Hypertensive or Hypotensive Emergency) And Safety Escape Criteria	Since the aim of the RADIANCE II study is to verify the effectiveness of renal denervation without medication changes confounding the results, it is intended that strict adherence to medication washout be maintained through the Primary Efficacy endpoint visit which occurs two months after randomization. However, in cases where antihypertensive medication changes are considered medically necessary (e.g. due to adverse events related to BP or BP medications or a significant change in BP), medication and/or doses may be adjusted according to the following guidelines: <u>High BP Action (inclusive of Hypertensive Emergency)</u> Clinical intervention may be required for patients who have clinical adverse events felt to be related to persistent or elevated hypertension defined by any of the following: • Average Home BP ≥170 mmHg systolic or ≥105 mmHg diastolic, and subsequently confirmed by an average Office BP ≥ 180 mmHg systolic or ≥ 120 mmHg diastolic. If an in-office blood pressure cannot be obtained due to the COVID-19 public health emergency, the Home BP Diary will be used to confirm the need for clinical intervention. • Daytime ABP ≥ 170 mmHg systolic or ≥ 105 mmHg diastolic **Prior to Randomization –** In the event of elevated BP as defined above (i.e. with associated clinical events felt to be related to persistent or elevated hypertension) prior to randomization, the subject will be treated per Institutional guidelines and withdrawn from the study (Safety Escape Criteria). **Post-Randomization –** In the event of elevated BP as defined above (i.e. with associated clinical events felt to be related to persistent or elevated hypertension), the treatment regimen should follow the hypertension medication escalation algorithm as described in

	Table 8.11-1. All changes in antihypertensive treatment will be documented and patient BP data will be included as per intention-to-treat. <u>Low BP Action (inclusive of Hypotensive Emergency requiring hospitalization)</u> Clinical intervention may be required for patients who have clinical adverse events felt to be related to persistent or reduced blood pressure as defined by any of the following: • Office Systolic BP reduced to <110 mmHg with associated signs and symptoms of hypotension, or • Reduced renal perfusion or an increase in creatinine ≥ 30% If an in-office blood pressure cannot be obtained due to the COVID-19 public health emergency, the Home BP Diary will be used to confirm the need for clinical intervention. The dosage of study-defined drugs can be reduced temporarily or discontinued permanently for subjects experiencing hypotension, as defined above. The order in which anti-hypertensive drugs should be discontinued will depend upon the stage that the subjects are within the scheduled FU and the status of drug escalation (if any). For all subjects in whom hypertension medication escalation has started since the 2-month FU visit, down-titration or discontinuation of antihypertensive medication should follow the reverse order in which they have been added such that the last drug added should be first stopped (followed by the penultimate drug etc.). All changes in antihypertensive treatment will be documented and patient BP data will be included as per intention-to-treat.
Cross-Over to Treatment	Following at least 12 months FU post-procedure, subjects assigned to the Control (sham) group may cross-over and receive treatment. Subjects who agree to cross-over will undergo a sponsor review to confirm cross-over eligibility. Eligibility to cross-over to treatment will be communicated to the site. Cross-over eligibility can be confirmed in the event that all of the following conditions are met: • The DSMB has not stopped the study due to safety concerns or indicated an increased safety risk associated with the treatment • The control subjects' BP remains uncontrolled at the point of cross-over (average daytime ambulatory systolic BP ≥ 135 mmHg and/or diastolic BP ≥ 85 mmHg • The subject agrees to the procedure • At time of cross-over, the patient does not meet any of the cross-over exclusion criteria (listed in Section 5.4). In the event of cross-over to treatment, subjects will be followed at 1, 2, 6, 12, 24, 36, 48 & 60 months post cross-over procedure.
Medication Compliance	Anti-hypertensive medication adherence will be assessed at Baseline (post washout/run-in), 2 months, 6 months and 12 months FU by detection of antihypertensive drug metabolite by urine analysis. For subjects that cross-over to treatment, urine will also be collected for anti-hypertensive drug metabolite analysis at Cross-over Baseline, 2 Month, 6 Month and 12 Month post cross-over procedure.
Primary Efficacy Endpoint	The Primary Efficacy endpoint is a reduction in average daytime ambulatory systolic BP from baseline to 2 months post procedure.

Primary Efficacy Endpoint Statistics	The average difference between randomized groups for the change in daytime ambulatory systolic BP at 2 months post-procedure will be compared by ANCOVA adjusted for subjects' baseline daytime ambulatory systolic BP. Tests will be performed at a 0.05 alpha level. For an assumed treatment effect (mean ± standard deviation) of 6±12 mmHg, with a 2:1 randomization, the planned sample size (n=225 will provide >90% power based on a two-sided 0.05 alpha and allows approximately 15% loss to follow-up.
Secondary Efficacy Endpoints	The statistical analysis of the Secondary Efficacy Endpoints will follow the methodology of the Primary Efficacy Endpoint: • Reduction in average 24-hr ambulatory systolic BP at 2 months post procedure. • Reduction in average office systolic BP at 2 months post procedure • Reduction in average home 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 office diastolic BP at 2 months post procedure • Reduction in average home diastolic BP at 2 months post procedure
Observational Efficacy Assessments	Additional observational assessments of effectiveness will be evaluated including but not limited to: • 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 • 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 • Percentage of subjects who are controlled in the absence of changes in hypertensive 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) • Percentage of subjects who are controlled including any changes in hypertensive 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) • 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 treatment score (number of antihypertensive drugs, doses, classes) 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 requiring initiation of anti-hypertensive drug therapy at any available timepoints post procedure
Primary Safety Endpoint	All adverse clinical events will be collected, coded and reported, for the duration of the study according to the definitions of ISO: 14155: 2011 (see Section 12.1). 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/m^2 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.
Primary Safety Endpoint Statistics	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 subject should provide 95% power for the performance goal if the population safety rate is approximately 3.0%.

Additional Safety Assessments	Additional assessments of safety will be evaluated including but not limited to: • Incidence of post procedure pain • Difference in average score on the Pain Numeric Rating Scale between pre-procedure and hospital discharge • Incidence of post procedure pain lasting > 2 days • Incidence of severe post procedural pain defined as a score of ≥ 8 on the Pain Numeric Rating Scale (if baseline score was ≤ 4) • Significant decline in renal function defined as ≥ 40% reduction in eGFR at 2, 6, & 12 months post procedure • Incidence of adverse events due to COVID-19
Pre-specified subgroup analysis	Post-hoc evaluations of efficacy will be evaluated in specific subgroups including but not limited to: • Sex • Race (Black versus non-black) • Age • Geography • Baseline ambulatory systolic BP • Baseline office systolic BP • Abdominal Obesity • Number of ablations performed
Overall Sample Size	Assuming a 2:1 randomization, 128 treated and 64 sham subjects were calculated as required to detect an absolute difference in daytime systolic ABP change from baseline to 2 months of 6 mmHg between Treatment and Control assuming a standard deviation of 12 mmHg, 90% power and a 2-sided 0.05 alpha. The estimated minimum sample size therefore to demonstrate efficacy is 192 subjects. To account for an approximate 15% rate of premature withdrawal or failure to reach the primary end point measure, and a desire to have sufficient numbers to support the Post-hoc evaluations of additional pre-specified cohorts, up to 225 subjects will be recruited and randomized.
Study Geographies	RADIANCE II will be conducted at up to 50 clinical investigational sites in the USA and up to 50 sites outside the USA. A minimum of 50% of randomized subjects will be included in the USA.
Study Duration	The expected duration, from initial enrollment to study closure, will be approximately 96 months.
Overall Subject Selection	Subjects following the indications/contraindications for use of the Paradise System with a documented history of hypertension eligible for antihypertensive therapy, will be identified from the general patient population by the enrolling center. In addition, subjects must meet all inclusion criteria and none of the exclusion criteria.
Inclusion Criteria:	Male and female subjects who meet the following criteria should be given consideration for inclusion: • Appropriately signed and dated informed consent • Age ≥18 and ≤75 years at time of consent • Documented history of hypertension • Previously or currently prescribed antihypertensive therapy

	• Average seated office BP ≥ 140/90 mmHg <180/120 mmHg at Screening Visit (V0) while stable for at least 4 weeks on 0-2 anti-hypertensive medications of different classes* • Able and willing to comply with all study procedures Subjects who meet the following criteria will be considered eligible for randomization: • Documented daytime ABP ≥ 135/85 mmHg and < 170/105 mmHg at Baseline Visit (V1) after 4-week washout/run-in period • Suitable renal anatomy compatible with the renal denervation procedure, documented by renal CTA or MRA of good quality performed within one year prior to consent (a CTA or MRA will be obtained in patients without a recent (≤1 year) cross-sectional renal imaging) and confirmed by renal angiogram in subjects that continue to procedure (see Exclusion Criteria) • Sinus rhythm at time of procedure **Potassium-sparing diuretics such as Amiloride hydrochloride and Triamterene may be prescribed in combination with another diuretic (e.g. a thiazide or loop diuretic) for their potassium conservation properties. In this situation, the diuretic combination is considered as a single class of anti-hypertensive.*
Exclusion Criteria:	Subjects who meet any of the following criteria will be excluded: • Renal artery anatomy on either side, ineligible for treatment including: o Main renal artery diameter < 3 mm or > 8 mm o Main renal treatable artery length < 20 mm (may include proximal branching) o A single functioning kidney o Presence of abnormal kidney tumors o Renal artery with aneurysm o Pre-existing renal stent or history of renal artery angioplasty o Pre-existing aortic stent or history of aortic aneurysm o Prior renal denervation procedure o Fibromuscular disease of the renal arteries o Presence of renal artery stenosis of any origin ≥ 30% o Accessory arteries with diameter ≥ 2 mm < 3 mm or > 8 mm* • Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter • Known, uncorrected causes of secondary hypertension other than sleep apnea • Evidence of active infection within 7 days of procedure • Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma HbA1c ≥ 9.0%) • Documented history of chronic active inflammatory bowel disorders such as Crohn's disease or ulcerative colitis • eGFR of <40 mL/min/1.73 m^2 (by Modification of Diet in Renal Disease formula) • Brachial circumference ≥ 42 cm • Any history of cerebrovascular event (e.g. stroke, transient ischemic event, cerebrovascular accident) • Any history of severe cardiovascular event (e.g. myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV) • Documented confirmed episode(s) of stable or unstable angina within 12 months prior to consent

	• Documented repeat (>1) hospitalization for hypertensive crisis within the prior 12 months and/or any hospitalization for hypertensive crisis within three (3) months prior to consent • Prescribed to any standard antihypertensive cardiovascular medication (e.g. beta blockers) for other chronic conditions (e.g. ischemic heart disease) such that discontinuation might pose serious risk to health in the opinion of the investigator • Documented history of persistent or permanent atrial tachyarrhythmia • Active implantable medical device (e.g. ICD or CRT-D; neuromodulator/spinal stimulator; baroreflex stimulator) • Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea. • Primary pulmonary hypertension • Documented contraindication or allergy to contrast medium not amenable to treatment • Limited life expectancy of < 1 year at the discretion of the Investigator • Night shift workers • Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or for any reason in the opinion of the investigator, would be unlikely or unable to comply with study protocol requirements or whose participation may result in data analysis confounders • Pregnant, nursing or planning to become pregnant within 12 months post procedure. Negative pregnancy test required, documented within a maximum of 7 days prior to procedure for all women of childbearing potential. Documentation of effective contraception is also required for women of childbearing potential • Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable) * *These inclusion/exclusion criteria may only be finally determined during the active renal angiogram procedure, subjects will therefore only count towards the enrollment ceiling at the time of randomization*
Study Administration	RADIANCE II will be run under the guidance of a Steering Committee comprising of International physicians with expertise in the areas of Renal Denervation, Vascular Medicine, Hypertension, Interventional Cardiology and Nephrology. An independent Data Safety Monitoring Board (DSMB) will also oversee the study activities from a safety perspective and pre-specified clinical events will be adjudicated by an independent Clinical Events Committee (CEC).
Ethics	The study will be conducted in accordance with the Declaration of Helsinki, ISO 14155:2011, FDA 21 CFR parts 50, 54, 56, 812, FDA 45 CFR part 46, and other applicable local and national regulations.

2. Introduction

2.1. *Hypertension and Clinical Need*

Hypertension is a major public health burden, present in more than one quarter of adults in developed societies and associated with reduced life expectancy and increased risk for cardiovascular disease, including myocardial infarction, stroke, and heart failure[i,ii]. At present, it accounts for approximately 9 million deaths worldwide annually[iii].

Currently the first line treatments for hypertension are recommendations for lifestyle modification (e.g. dietary restrictions including salt, caffeine, and alcohol; increased exercise and reduced smoking), and the use of antihypertensive medication. Guidelines typically recommend the use of one or two drugs of different classes[iv] but despite the well documented ability of hypertensive drugs to reduce blood pressure (BP), particularly in combination,[v] hypertension remains uncontrolled in as much as 50% of patients in the United States with even higher rates in Europe. Inability to control hypertension may be caused by multiple factors including inadequate or inappropriate treatment, poor medication adherence[vi,vii] and in a small subset of patients, hypertension which is truly non-responsive to conventional therapies- a condition known as resistant (or refractory) hypertension. The European Society of Hypertension defines resistant hypertension as BP that remains above goal despite treatment with a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses.[iv] While it has not been specifically determined whether treatment of resistant hypertension provides greater overall clinical benefit than treatment of more easily controlled hypertension, it is very well-established that reduction in blood pressure and hypertension control, improve cardiovascular morbidity and mortality and provide substantial clinical and economic benefit.[viii]

2.2. *Other Therapeutic Options*

Currently therapeutic options outside the use of standard classes of antihypertensive medications are limited[ix] prompting the exploration of interventional approaches to provide complementary therapeutic tools.

2.3. *Role of the Sympathetic Nervous System*

Animal studies and subsequent studies in humans have demonstrated that the sympathetic nervous system, in particular afferent and efferent sympathetic nerves from and to the kidneys, plays an important role in BP regulation and the pathophysiology of hypertension.[x,xi] In certain patient subsets, activity of the afferent and efferent sympathetic nerves in the renal artery walls may be the primary mechanism by which the kidneys contribute to systemic hypertension.

The disruption of activity in the renal nerves has been shown to prevent, delay, or reduce the magnitude of hypertension in a wide variety of animal models.[xii,xiii] These results were extended to humans during the mid-century through experience with surgical sympathectomy (splanchnicectomy), a major, invasive procedure that reduced BP at the cost of significant operative mortality, and which was abandoned with the advent of effective pharmacotherapy.[xiv]

Despite an unacceptable risk profile, surgical sympathectomy did demonstrate proof-of-concept for complete sympathetic denervation in the treatment of hypertension and set the stage for modern, more targeted, treatment modalities.[xv] Amongst these are a therapeutic system for baro-reflex activation, which modifies afferent sympathetic nerve activity via stimulation of the carotid sinus nerves (the Rheos Baroreflex Hypertension Therapy System - CVRx Inc, Minneapolis, MN, USA), targeted injection of neurotoxic agents directly into the perivascular layer of the renal artery wall (e.g. Ablative Solutions PeriVascular Renal Denervation system, Menlo Park, CA, USA) and minimally invasive interventional approaches to renal sympathetic denervation therapy, accomplished via catheter-based percutaneous denervation procedures targeting the renal nerves in patients with resistant hypertension.[xvi,xvii,xviii,xix]

2.3.1. Percutaneous Renal Denervation Therapy

Disruption of the afferent and efferent sympathetic nerve bundles via a catheter-mounted probe was originally investigated as a treatment for resistant hypertension using radiofrequency (RF) energy. The original product for this indication was the Symplicity® Flex Catheter System™ (Ardian Inc., Palo Alto, CA, USA), which received CE mark in Europe in 2008. The device is powered by an external RF generator and consists of a catheter tipped with a 2mm electrode that delivers RF energy directly to the renal arterial wall at multiple discrete locations in an attempt to transmurally ablate focal sympathetic nerves.

In order to overcome some of the technique and technical limitations with earlier RF systems, Medtronic (Fridley, MN, USA) has more recently been testing the use of the Symplicity Spyral™ multi-electrode renal denervation catheter. This updated system incorporates multiple electrodes and is being evaluated for use both within the main renal artery and in the distal branches[xx,xxi]

The ReCor Medical Paradise Renal Denervation System is differentiated from the RF systems in that it uses ultrasound energy delivered circumferentially to the adventitia, thus sparing the renal arterial wall, while still ablating the sympathetic nerves.

2.4. *Current Status of Renal Denervation Clinical Evidence*

The early primary clinical data supporting percutaneous RF renal denervation came primarily from single arm studies evaluating the performance of the Symplicity Flex catheter [xvii,xviii,xix,xxii,] although both the Vessix[xxiii] (Vessix Vascular Inc. Laguna Hills, VA, USA) and EnligHTN[xxiv] St Jude Medical, St Paul, MN, USA) RF Systems also had some level of clinical evidence supporting them. More recently randomized, blinded, sham-controlled studies of renal denervation effect have become more standard. ReCor Medical and Medtronic have ongoing research programs utilizing their respective renal denervation systems in randomized, sham-controlled clinical trials in patients on antihypertensive medications and in patients withdrawn from anti-hypertensive medications.

2.4.1. Symplicity HTN-3

The Symplicity HTN-3 trial was the first randomized, blinded and sham- controlled safety and efficacy evaluation of the Symplicity catheter conducted in the US. A total of 535 patients whose baseline office systolic BP was ≥160 mmHg despite treatment with maximum tolerated doses of at least 3 antihypertensive drugs including a diuretic, were randomized 2:1 to renal denervation versus sham control with the sham consisting of a renal angiogram procedure. The primary efficacy endpoint for HTN-3 was the change in office systolic BP at 6 months with a secondary endpoint related to change in mean 24-hr ambulatory systolic BP.[xxv] The data from HTN-3 demonstrated that despite an office systolic BP drop at 6 months of -14.1 mmHg in the treatment arm, there was also a substantial average drop in BP in the sham arm of -11.7 mmHg, such that the difference between arms was not statistically significant. A similar trend was observed with ABP data where the actual difference in systolic BP drop between arms was < 2mmHg[xxvi]. Despite the lack of significant effectiveness of the treatment versus sham, the safety endpoint was passed with no documented difference in safety risk between groups as defined per protocol. The outcome of the HTN-3 trial was unprecedented based on the early data from single-arm studies and resulted in the development of a number of guidelines which drove the design and implementation of current renal denervation clinical trials[xxvii,xxviii].

2.4.2. The Renal Denervation for Hypertension (DENERHTN) Trial

In 2015 a French Ministry of Health-sponsored study of the Symplicity Catheter (DENERHTN) was published in Lancet.xxix The study evaluated the effect of RF renal denervation in resistant hypertensive patients uncontrolled on a standardized, stepped-care, antihypertensive treatment regimen versus patients uncontrolled on the same standardized hypertensive treatment alone. The trial was double blind and placebo-controlled and was designed and conducted by clinical centers in France specialized in hypertension management. Initially patients were stabilized for 4-6 weeks on a fixed dose, triple combination antihypertensive regimen consisting of Indapamide (1.5 mg), Amlodipine (10 mg) and Ramipril 10 mg or Irbesartan (300 mg). If patients remained hypertensive on this therapy regimen, they were then randomized 1:1 to renal denervation or standardized therapy alone. A total of 1416 patients were screened to enroll and randomize 106 patients. Patients were initially followed for 6 months and a predefined antihypertensive medication escalation protocol was in place for both groups to ensure that patients were not allowed to remain hypertensive for extended periods of time and to allow calculation of comparative drug burden. The primary endpoint of the study was a difference in daytime ABP between groups with office and home BP differences as secondary analyses. At 6 months, DENERHTN demonstrated that the mean decrease in daytime systolic ABP was statistically greater in patients randomized to renal denervation plus standardized therapy versus standardized therapy alone. In addition, the percentage of patients controlled at the 6 month FU visit, was higher in the renal denervation group for daytime, night-time and 24-hr ABP. Until recently, DENERHTN was the only blinded, placebo-controlled, evidence demonstrating a significant effect of renal denervation in resistant hypertension.

2.4.3. SPYRAL ON and OFF MED Trials

The more recent developments in the field of device-based renal denervation has been the conduct of a series of well-controlled clinical studies in accordance with clinical consensus recommendations. The SPYRAL HTN-ON MED and SPYRAL HTN-OFF MED studies feature next-generation renal denervation RF technologies that are tested in randomized, sham-controlled settings[xx,xxi]. The SPYRAL HTN-ON MED study tests the use of the Symplicity Spyral system in patients on antihypertensive medications, and this study is ongoing with results yet to be published. In the recently published SPYRAL HTN-OFF MED trial[xxi], patients were taken off their antihypertensive medication until the 3-month primary endpoint of between-group difference in 24-hr ambulatory systolic BP could be captured. The study showed that the procedure was generally safe, with no major adverse events (MAEs) in either group. The renal denervation arm had a bigger drop in 24-hr systolic BP than the sham (-5.5 vs. -0.5 mm Hg, respectively; P=0.0414), with a between group difference of -5.0 mm Hg (95% CI of -9.9 to -0.2 mm Hg). This study is being used by the sponsor to design a follow-up pivotal trial.

3. Summary of ReCor Medical Studies

3.1. *Paradise Clinical Study Summary*

First in human evidence of the clinical safety and efficacy of the Paradise System was initially evaluated in the first-in-man REnal Denervation by Ultrasound transCatheter Emission (REDUCE) Trial, a single-center feasibility study initiated in 2011 and conducted at Vergelegen Medi-Clinic, South Africa[xxx]. Subsequently, two multi-center, ReCor Medical Inc. sponsored post-market evaluations (the REALISE and ACHIEVE studies) were initiated in 2012, and 2013, respectively. In 2016, the RADIANCE HTN Study, a randomized, double-blind, two-cohort study evaluating the efficacy of the Paradise System in both primary hypertensive patients washed out of antihypertensive medications (SOLO Cohort) and resistant hypertensive patients (TRIO Cohort), was initiated. Recently the SOLO cohort completed randomization and 2-month FU, while the TRIO Cohort continues to include subjects.

3.2. *The ACHIEVE Study*

The TrAnsCatHeter Intravascular ultrasound Energy delivery for rEnal denervation (ACHIEVE study) was a post market study that enrolled patients with severe resistant hypertension at eight sites in Sweden, Germany, and the Netherlands. Ninety-six (96) subjects were treated and followed for 12 months. Measurement of office BP was required at 3, 6 and 12 month FU visits and optional at 1 month. Recordings of 24-hr ABP was required at a minimum, for all patients at 6 and 12 months post treatment. The mean age of enrolled patients was 64 years and 59% were male. Baseline comorbidities and cardiovascular risk factors included type II diabetes mellitus (40%), history of peripheral vascular disease (8%), history of stroke (10%), history of myocardial infarction (24%), history of obstructive sleep apnea (21%), and prior renal denervation (1%). The mean office systolic BP at baseline was 176±21 mmHg (n=95) and mean 24-hr ABP at baseline was 156±15 mmHg (n=91). Ninety-five (95) patients completed the 3 months FU, 92 completed 6 months FU and 87 completed 12 months FU. Results in the

Intention to Treat (ITT) population demonstrate a mean systolic office BP drop of -15 mmHg at 12 months (n=80, P<0.001). In the same population, mean 24-hr ABP drops were -7 mmHg at 12 months (n=76, P< 0.0007). During the study there was a single patient with an event meeting the MAE definition: a hospitalization for hypertensive crisis within 1 month of the procedure. Of note, within 1 month of the procedure there were no cases of mortality, renal failure (eGFR < 15 or need for dialysis), embolic event resulting in end-organ dysfunction, renal perforation or dissection requiring intervention, or access site complication requiring repair or transfusion. There were also no cases of new stenosis > 70% within 6 months. Five of 96 patients (5.2%) had minor groin complications not meeting the MAE definition. In the entire study follow-up there was one patient death due to a presumed myocardial infarction approximately 3 months after the procedure; this event was deemed to be unrelated to the device or procedure.

3.3. *The RADIANCE HTN Study*

The RADIANCE HTN study is a randomized, double-blind, sham-controlled, 2-cohort study [Initial IDE G150144] designed to demonstrate efficacy and document the safety of the Paradise Renal Denervation System in two distinct populations of hypertensive subjects[xxxi]. The SOLO cohort completed recruitment on December 28th 2017 and included subjects with primary hypertension on 0-2 antihypertensive drugs that were washed out for a period of 4 weeks prior to randomization. The TRIO cohort is ongoing and includes subjects with resistant hypertension who have had their current antihypertensive medication replaced by a single pill, triple, fixed-dose antihypertensive medication regimen. In both cohorts, the primary efficacy endpoint is the between-group difference in 2 month change in daytime ambulatory BP.

In the SOLO cohort, a total of 146 subjects were randomized to renal denervation (N=74) or sham procedure (renal angiogram) (N=72). In the Intention to treat (ITT) population, renal denervation reduced daytime ambulatory systolic blood pressure more than the sham procedure (-8.5 mm Hg vs. -2.2 mm Hg; baseline-adjusted difference: -6.3 mm Hg, 95% CI -9.4 to -3.1, P<0.001). Consistent reductions were observed for daytime diastolic, and 24-hr ambulatory systolic and diastolic BPs. Fewer subjects in the renal denervation group received antihypertensive medication prior to 2 months compared with the sham group [5/74 (6.8%) vs. 13/72 (18.1%), P=0.04]. Among subjects in the renal denervation group, 15/74 (20.3%) attained controlled 2-month daytime ambulatory BP (<135/85 mm Hg) in the absence of antihypertensive medications, vs. 2/72 (2.8%) in the sham group (P=0.001). A per protocol analysis was also completed which excluded the following subjects: 1) subjects not meeting baseline daytime ABP or renal anatomy inclusion criteria, 2) subjects in the denervation group who did not receive bilateral denervation, 3) subjects we were treated with antihypertensive medication before the 2-month ABP measurement and 4) subjects who did not compete the 2-month ABP assessment. By removing these confounding, especially those of antihypertensive medication restarts. The per protocol differences are even larger (daytime between group 2-month ambulatory systolic difference of -8.2 mm Hg; P<0.001).

In the RADIANCE-HTN SOLO Study, subjects remained blinded through the 6-month follow-up visit. Between 2 months and 6 months, a standardized stepped-care antihypertensive

treatment (SSAHT) was initiated wherein one medication was added each month based on home blood pressure ≥135/85 mmHg, with the goal of achieving blood pressure control. A total of 69/74 treated (RDN) patients and 71/72 sham patients completed the 6-month ambulatory BP measurement. At 6 months, 65.2% of patients in the treated group were treated with a standardized stepped-care antihypertensive treatment vs. 84.5% in the sham group (p=0.008) and the average number of antihypertensive medications and defined daily dose were less in the RDN group than in the sham group (0.9 vs. 1.3, p=0.010 and 1.4 vs. 2.0, p=0.018; respectively). Despite less intensive SSAHT, RDN reduced daytime ambulatory systolic BP to a greater extent than sham (-18.1±12.2 vs. -15.6±13.2 mmHg, respectively; difference adjusted for baseline BP and number of medications: -4.3 mmHg, 95% confidence interval, -7.9 to -0.6, p=0.024). There were no major adverse events in either group through 6 months.

All subjects were unblinded following the completion of the 6-month ambulatory BP measurement and were subsequently managed with antihypertensive medications per physician discretion. As such, the 12-month timepoint represents the effect of renal denervation vs. sham control in the presence of standard of care medication management. A total of 65/74 RDN patients and 67/72 sham patients completed the 12-month ambulatory blood pressure measurement. At 12 months, 72.3% of RDN patients were on antihypertensive medications vs. 85.1% with sham (p=0.073); the average number of medications and defined daily dose were less with RDN vs. sham (1.0 vs. 1.4, p=0.015; 1.4 vs. 2.2, p=0.007; respectively). Despite less intensive treatment, the decrease in daytime ambulatory systolic BP from baseline was stable between 6 and 12 months, reaching -16.5±12.9 mmHg in the RDN group vs. -15.8±13.1 mmHg in the sham group at 12 months (adjusted difference: -2.3 mmHg, 95%CI, -5.9 to 1.3 mmHg, p=0.201). The between group adjusted difference was -6.3 (-11.1 to -1.5) mmHg for office SBP (p=0.010) and -3.4 (-6.9, 0.1) mmHg for home SBP (p=0.062) in favor of RDN. There was 1 non-cardiovascular death and 1 cerebrovascular event in the sham group and no other major adverse events in either group through 12 months. Compared with a sham procedure, the BP lowering effect of ultrasound RDN was maintained at 12 months with less prescribed antihypertensive medications.

3.4. *Device System Overview*

The ReCor Medical Paradise Ultrasound Renal Denervation System (Paradise System) is CE-marked in countries accepting the CE mark, but Investigational in the USA.

The system is a catheter-based device designed to use ultrasound energy to thermally ablate the afferent and efferent nerves surrounding the renal artery and serving the kidney. Key features which differentiate ultrasound energy from RF energy are:

- Direct tissue contact with the ultrasound energy source is not required for energy transmission, minimizing the risk of overheating the arterial wall with consequent tissue damage

- The absorption of ultrasound by liquids (including blood) is minimal, thereby potentially avoiding the risk of thrombogenicity that may occur when a RF energy source loses contact with the vessel wall
- Ultrasound provides controlled energy delivery independent of catheter positioning or tissue characteristics
- Ultrasound provides a controllable ablation profile via manipulation of duration and intensity of the energy delivery combined with changes in cooling flow rate
- The uniform circumferential heating possible with ultrasound reduces the number of treatment sites required to achieve renal nerve ablation, minimizing energy delivery and improving ease of use

The Paradise System consists of two main components: a single use Paradise Catheter, containing an ultrasound energy source (transducer) and a portable Paradise Generator, which powers the transducer. The Paradise Catheter is introduced via femoral access under fluoroscopic guidance and advanced into the renal artery. Bilateral renal denervation is achieved by delivering ultrasound energy within each renal artery.

The Paradise System also includes two ancillary components allowing the delivery of fluid and power to the main components, all of which are used within the scope of their labeling:

- **Paradise Cartridge** when used in conjunction with the Generator, controls the closed-loop cooling fluid flow through the Catheter
- **Paradise Connection Cable** allows for the communication of transducer information, such as operating frequency and power, from the Catheter to the Generator as well as the transfer of electrical energy during the procedure

Table 3.4-1, identifies the components of the Paradise System and their basic attributes.

Table 3.4-1: Paradise System Components

Identification	Paradise System (PRDS) Component	Sterile	Reusable	Blood Contact
PRDS-063-02	PRDS Catheter (3.5 mm balloon diameter)	Yes	No	Yes
PRDS-064-02	PRDS Catheter (4.2 mm balloon diameter)			
PRDS-065-02	PRDS Catheter (5 mm balloon diameter)			
PRDS-066-02	PRDS Catheter (6 mm balloon diameter)			
PRDS-067-02	PRDS Catheter (7 mm balloon diameter)			
PRDS-068-02	PRDS Catheter (8 mm balloon diameter)			
PRDS-USG-02	Paradise Generator	No	Yes	No
PRDS-CT-02	Paradise Cartridge	Yes	No	No
PRDS-CC-02	Paradise Connection Cable	Yes	No	No

3.5. *Main Components of the Paradise System*

3.5.1. The Paradise Catheter

The Paradise Catheter consists of a single use, multi-lumen catheter shaft with a cylindrical piezoelectric ceramic transducer inside an inflatable balloon at the distal end of the catheter. The cylindrical transducer converts the electrical energy to ultrasound energy, which is then radiated into the renal artery tissue. Located at the proximal end of the catheter, is a hub that connects electrical and fluid pathways. The Paradise Catheter (Figures 3.5-1 & 3.5-2) is available in 3.5, 4.2, 5, 6, 7, and 8 mm balloon sizes.

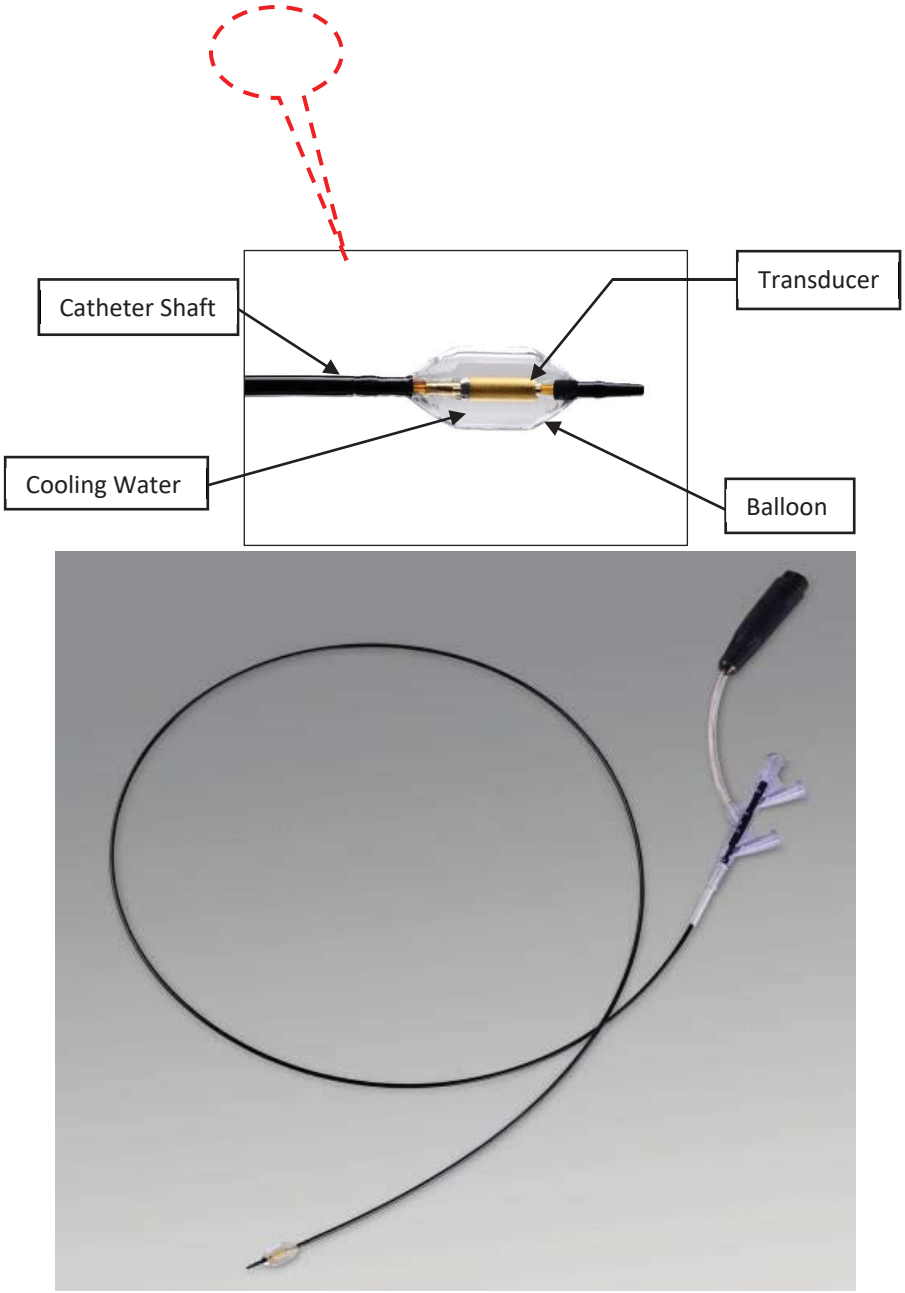
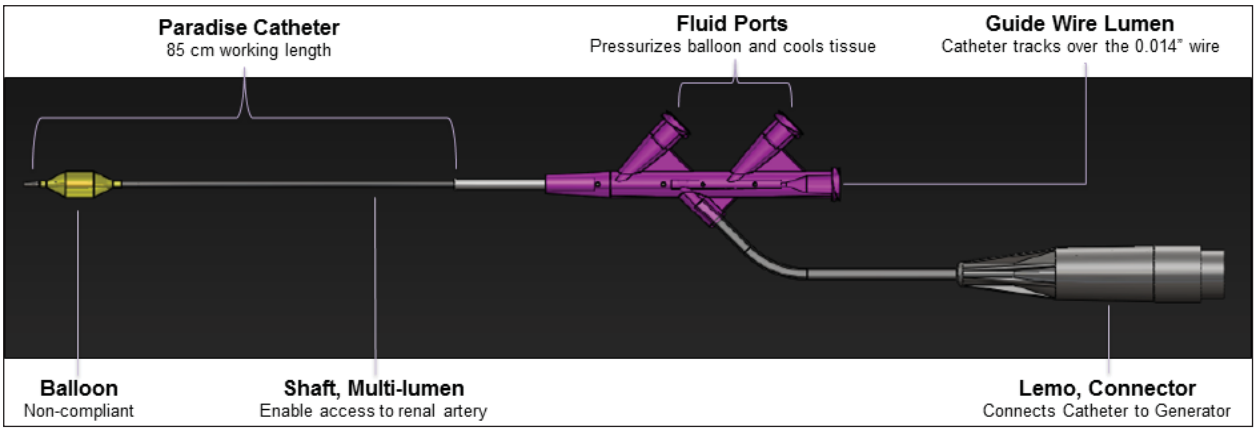


Figure 3.5-1: The Paradise Catheter with Magnified Detail of Ultrasound Source

Figure 3.5-2. Paradise Catheter Features



Each Paradise Catheter has a programmed memory chip (EEPROM) that communicates to the Paradise Generator to automatically set the power level (Watts) and frequency (MHz) required to treat various diametric sizes of renal arteries. The physician selects the Paradise Catheter with appropriate balloon size based on measuring the renal artery size using standard medical angiographic techniques.

3.5.2. The Paradise Generator

The Paradise Generator is designed to control energy delivery and fluid management of the Paradise System to ensure proper therapy. The Paradise Generator contains all of the electronics and fluid controls for the device as well as a user interface on the front panel. On the Paradise Generator front panel, the user can control all operating stages of the Paradise System, including catheter balloon inflation and deflation, and initiating or discontinuing therapy. The duration of energy delivery is programmed into the Paradise Generator software and is not a parameter that can be changed by the user. Each Catheter's power level (Watts) and the Generator's duration (seconds) is what comprises the Paradise System energy dose.

The Generator interfaces with a Paradise Cartridge to provide sterile fluid to the Catheter for inflating and deflating the catheter balloon and aiding in the delivering of the therapy. The Paradise Generator is connected to the Paradise Catheter through the Paradise Cartridge and the Paradise Connection Cable. Electrical energy is delivered from the Generator through the Catheter, at which point, the electrical energy is converted to ultrasound energy via a piezoelectric transducer. Ultrasound energy is then transferred into the renal artery tissue which converts to heat and ablates the renal artery nerves.

Figure 3.5-3 below illustrates the Paradise Generator and accessories.

Figure 3.5-3. Paradise Generator and Accessories

The Paradise Cartridge attaches to the Generator and the Catheter. The Cartridge manages the flow of sterile water and the monitors the pressure within the catheter's balloon. The monitored pressure is communicated to the Paradise Generator and the Generator will adjust fluid flow to maintain accurate catheter balloon pressure throughout all of the System operating stages.

3.5.3. The Paradise Cartridge

The Paradise Cartridge is an accessory that is designed to support the procedural needs and functional operation of the Paradise System. When the Paradise Cartridge is used in conjunction with the Paradise Generator, it controls the sterile fluid flow into and out of the Paradise Catheter in a close-loop system. The fluid flows through the Cartridge and the Catheter body to the balloon at the catheter's distal tip and returns to the Cartridge. The integrated tubing is comprised of two distinct lumens and is 3 meters in length. The integrated tubing connects the Cartridge to the catheter's proximal end. The connectors at the Cartridge's distal end are reversible so that the orientation of connection to the catheter is universal.

The Paradise Cartridge attaches to the Generator and the Catheter. The Cartridge manages the flow of sterile water and the monitors the pressure within the catheter's balloon. The monitored pressure is communicated to the Paradise Generator and the Generator will adjust fluid flow to maintain accurate catheter balloon pressure throughout all of the System operating stages. Figure 3.5-4 illustrates the Paradise Cartridge.

Figure 3.5-4. Paradise Cartridge Diagram

The Paradise Connection Cable (as shown in Figure 3.5-5) provides the electrical connectivity between the Generator and the Catheter.

Figure 3.5-5. Paradise Connection Cable Diagram

3.6. *Non-investigational Components of the Paradise System*

3.6.1. Sterile Water

Sterile water is required to be connected to the Paradise Cartridge. The following water is recommended for use:

- Baxter 2B0304 Sterile Water for Injection (1000/250 ml)
- Wasser für Testzwecke et190 (Austria)
- B Braun Ecobag 75/12610321/0111
- B Braun L8500 (1000/250 ml)

3.6.2. Guide Catheters

The Paradise Catheter is introduced into the body using a commercially available guide catheter of minimum internal diameter 0.081" and 55 cm length. Guide Catheters/Sheaths that are recommended include, but are not limited to:

- Medtronic Launcher RDC tip (7 or 8 French; 55 cm)
- Medtronic MP1 (7 or 8 French; 55 cm)
- Medtronic IMA (7 or 8 French; 55 cm)
- Medtronic SCR (7 or 8 French; 55 cm)
- Cordis Vista Brite-Tip RDC (8 French; 55 cm)
- Terumo Destination® Guiding Sheath (6 French; 45 cm)

The following Guide Catheters are not recommended for use:

- Boston Scientific Mach 1 series (7 or 8 French)

3.6.3. Guide Wires

Any 0.014", 190 cm, heavy or middle weight commercially available guide wire may be used with the Paradise Catheter.

3.6.4. Hemostasis Valve

A non-threading hemostasis valve is recommended to ensure appropriate fluid flow through the catheter. The following hemostasis valve is recommended for optimal Paradise System function:

- Merit Medical Honor hemostasis valve (P/N MAP300)

3.7. *Principles of Operation*

The Paradise System utilizes therapeutic ultrasound energy consisting of high-frequency sound waves (i.e. rapid mechanical oscillations) that generate frictional heating in soft tissues. Due to the physics of sound propagation, direct tissue contact with the ultrasound source is not required for energy transmission. Therefore, a balloon-based fluid transfer mechanism is implemented for cooling the endothelial and medial layers of the arterial wall to preserve the integrity of the arterial wall during the energy delivery process. The Paradise System utilizes a cylindrical ultrasound source (the transducer) which creates uniform toroidal lesions with controllable geometries. By optimizing the size, shape and location of the lesion, denervation can be maximized while protecting the arterial intimal and medial layers.

The target thermal profile for energy delivery includes near-field and far-field cooled zones, to minimize endothelial or medial cell damage and to ensure there is no damage to non-target tissues beyond the targeted tissue region. The target ablation zone is located approximately 1-

6 mm from the arterial lumen where the accumulated thermal dose rises sufficiently to achieve cell death. Optimization of the tissue thermal profile can be achieved through management of the power delivered to the transducer, the duration of energy delivery, and the cooling flow rate.

The Paradise Catheter is intended to be employed in a catheterization laboratory under fluoroscopic guidance via femoral access only. The catheter is deployed into the renal artery through a delivery catheter inserted into the femoral artery near the groin and advanced to the descending aorta.

The Paradise Catheter is a minimally invasive device, remaining inside the body, in contact with the blood and the blood vessel walls for the duration of a typical catheterization laboratory procedure (less than one hour). It is supplied sterile and intended for a single use.

Appropriate systemic anticoagulation should be administered prior to procedure and verified by ACT or similar testing (e.g., ACT of 200, 250, or 300s depending on local guidelines). There are no specific post-treatment recommendations.

3.8. *System Labeling*

The Paradise System is CE-marked and labelled for "renal denervation" in countries accepting the CE mark for use, but is Investigational in the United States.

For this clinical study, the Paradise System will display the following labelling, as required by United States regulation:

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use.

4. RADIANCE Study Purpose and Objectives

4.1. *Study Objective*

The objective of the RADIANCE II Pivotal study is to demonstrate the effectiveness and safety of the Paradise System in subjects with Stage 2 hypertension on 0-2 anti-hypertensive medications of different classes at the time of consent. Prior to randomization, subjects will be hypertensive in the absence of hypertension medication. Subjects with no history of treatment with antihypertensive medications will be excluded. Study endpoints have been formulated to support these objectives.

4.1.1. Primary Efficacy Endpoint (2 month FU)

The Primary Efficacy Endpoint will be a reduction in average daytime ambulatory systolic BP at 2 months post procedure.

4.1.2. Secondary Efficacy Endpoints (2 month FU)

The Secondary Efficacy endpoints will be evaluated following the same statistical methodology as the Primary Efficacy Endpoint:

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

4.1.3. Observational Efficacy Assessments

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

- 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
- 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
- Percentage of subjects who are controlled in the absence of changes in hypertensive 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)
- Percentage of subjects who are controlled including any changes in hypertensive 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)
- 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 treatment score (number of antihypertensive drugs, doses, classes) at 6 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 requiring initiation of anti-hypertensive drug therapy at any available timepoints post procedure

4.2. *Primary Safety Endpoint*

All adverse clinical events will be collected, coded and reported, for the duration of the study according to the definitions of ISO: 14155: 2011 (see Section 11.1).

The primary safety endpoint is defined as a patient level composite of the incidence of the following events 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 composite MAE for the treatment arm will be compared to a performance goal, of 9.8%, as defined in the SYMPLICITY HTN-3 study [xxv]. This performance goal is the most relevant comparator as there is precedence for its use in a blinded, sham-controlled renal denervation study.

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

4.2.1. Additional Safety Assessments

- 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 Pain Numeric Rating 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
- Incidence of adverse events due to COVID-19

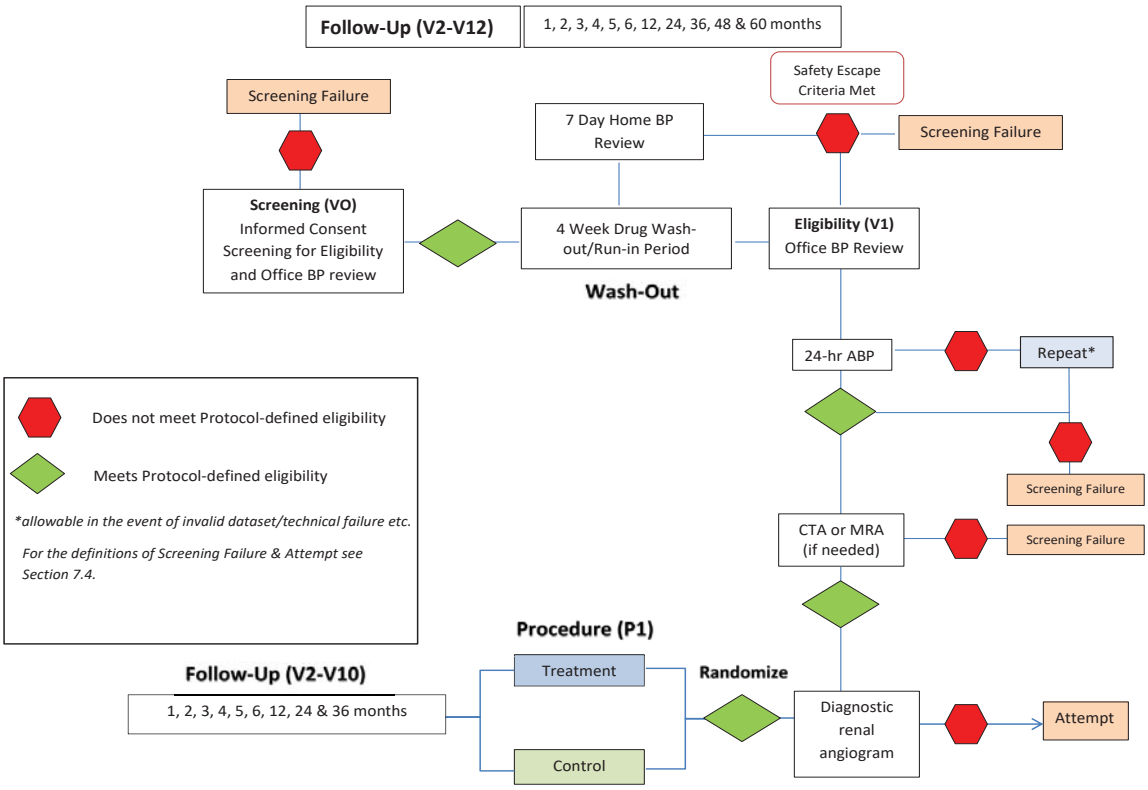
5. Design

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. The study will be conducted in up to 50 clinical investigational sites in the USA and up to 50 outside the USA. A minimum of 50% of randomized subjects will be enrolled in the USA.

5.1. *Duration*

The RADIANCE II Study will randomize up to 225 randomized subjects who will be followed in accordance with the study protocol for 60 months post procedure. It is anticipated that the duration of the study will be approximately 96 months. Figure 5.1.1 documents the study flow.

Figure 5.1-1: RADIANCE II Study Design



5.2. *Treatment and Control Assignment*

The RADIANCE II Study is a randomized study requiring treatment (renal denervation) and control (sham) assignments. Subjects meeting all the inclusion criteria and none of the exclusion criteria will be assigned in a 2:1 (Treatment: Sham) scheme. Subjects will be considered to count towards the randomization ceiling at the point of randomization independent of whether they undergo a successful procedure or not (see Section 7.4 for subject classifications).

5.3. *Blinding*

All subjects will be blinded up to the 12 Month FU. Specifically:

- Subjects will be blinded during the procedure by ensuring sedation occurs prior to randomization. In addition, unless the subject is under general anesthesia, headphones and eye covers will be used.
- Procedure scripts will be provided for Control (sham) procedures
- A blinding index[xxxii] will be used to evaluate the success of subject blinding. The blinding index will be evaluated post-procedure but prior to Discharge and also at 2-, 6- and 12-months FU.

Study personnel responsible for the measurement and upload of ABP post randomization will be blinded. To ensure patient safety, it is strongly recommended that the Discharge evaluation be completed by unblinded site personnel aware of the details of the procedure. Alternatively, blinded site personnel trained on the device and aware of potential adverse events related to the device and/or procedure may conduct the Discharge assessment. To reduce the potential for bias, it is strongly recommended that site personnel blinded to a subjects' randomization continue to be responsible for blood pressure measurements even after the patient is unblinded at the 12-month follow-up.

All Efficacy Endpoint data will be handled directly through the ABP core lab and independent statistician(s). Due to the nature of their support role, Sponsor representatives may be un-blinded to a limited number of randomizations due to presence at Procedures and/or during monitoring (see Sections 16.4 and 17.1). In the event of device deficiency, adverse device effects or serious adverse device effects, the Sponsor may become aware of the randomization of a specific subject but there will be no connection to outcome primary Efficacy data. The DSMB will be blinded to all primary efficacy data unless specific criteria for un-blinding are met.

5.4. *Cross-Over to Treatment*

Following at least 12 months follow-up post-procedure, subjects randomized to the Control (sham) group may cross-over and receive treatment. Subjects who agree to cross-over will undergo a sponsor review to confirm cross-over eligibility. Eligibility to cross-over to treatment will be communicated to the site. Cross-over eligibility can be confirmed in the event that all of the following conditions are met:

- The DSMB has not stopped the study due to safety concerns or indicated an increased safety risk associated with the treatment
- At the time of Cross-Over Baseline Eligibility (COV1), the subjects' average daytime ambulatory systolic BP is ≥ 135mmHg and/or diastolic BP ≥ 85mmHg
- The subject agrees to the cross-over procedure
- At time of cross-over, the patient does not meet any of the following exclusion criteria:

- Renal and/or renal artery anatomical exclusion criteria
- Evidence of active infection within 7 days of procedure
- Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter
- Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma Hb1Ac ≥ 9.0%)
- Any cerebrovascular event (e.g. stroke, transient ischemic event, cerebrovascular accident) within 3 months prior to cross-over baseline visit (COV1)
- Any severe cardiovascular event (myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV) within 3 months prior to cross-over baseline visit (COV1)
- Documented confirmed episode(s) of stable or unstable angina within 3 months prior to cross-over baseline visit (COV1)
- Hospitalization for hypertensive crisis within the 3 months prior to cross-over baseline visit (COV1)
- Active implantable medical device (e.g. ICD or CRT-D; neuromodulator/spinal stimulator; baroreflex stimulator)
- Pregnant, nursing or planning to become pregnant within 12 months post cross-over procedure. Negative pregnancy test required, documented within a maximum of 7 days prior to procedure for all women of childbearing potential. Documentation of effective contraception is also required for women of childbearing potential

Subjects that cross-over to treatment will be followed according to the cross-over visit schedule (see Table 8.1-2).

5.5. *Sample Size Rationale and Statistical Power*

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;
two sample means test=diff
mean diff = 6
std dev = 12
alpha = 0.05
power = 0.90
groupweights = (2.1)
n total = . ;
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 approximate 15% inflation is used so the total number of randomized subjects is 225 subjects.

5.6. *Justification for the Study Design*

The Simplicity HTN-3 pivotal trial[xxvii, xxix] was able to demonstrate safety of RF renal denervation in drug resistant hypertensive patients, but unable to demonstrate efficacy due to multiple study design confounders. Subsequently however, using a strictly standardized protocol and an ABP outcome measure, the DENERHTN study was able to show a decrease in daytime systolic ABP that was statistically greater in patients randomized to renal denervation plus standardized therapy than standardized therapy alone. More recently the SPYRAL OFF feasibility study and the RADIANCE-HTN SOLO Cohort, have shown that RF and ultrasound renal denervation respectively, can cause significant reductions in ABP in primary hypertension patients treated in the absence of antihypertensive medications. In addition, both studies demonstrate that the renal denervation procedure appears to be low risk but unlike Symplicity HTN-3, neither SPYRAL OFF nor RADIANCE-HTN SOLO were powered to confirm safety.

5.6.1. RADIANCE II Justification

The RADIANCE-HTN SOLO cohort, demonstrated the ability of the Paradise ultrasound renal denervation to significantly reduce BP in subjects hypertensive in the absence of antihypertensive medication however, the study was not designed or powered to demonstrate safety. Based on that, RADIANCE II has been designed to complement and expand the effectiveness data collected from the RADIANCE HTN SOLO cohort and to increase the sample size of treated subjects in order to justify and demonstrate safety. Subjects with uncontrolled hypertension at consent, will be randomized in the absence of any antihypertensive drugs in line with the prior design of the SOLO cohort. This will again, allow the effectiveness of ultrasound renal denervation to be evaluated without the confounding influence of drugs either from a pharmacological or patient compliance perspective. The patient population to be included in RADIANCE II is also in line with those subjects included in the SOLO cohort and has been defined to minimize any risk of cardiovascular events including stroke. The time period that subjects are taken off their antihypertensive medications is limited and in line with the short-term study designs typically used to evaluate new antihypertensive therapy against placebo control.[xxxiii] Additionally, safety and efficacy data collected from the SOLO cohort, appear to justify the potential risks associated with this study design.

RADIANCE II will aim to verify and expand on early efficacy data collected in RADIANCE HTN and hence a difference in daytime systolic ABP between sham and treatment groups, 2 months post procedure has been selected as the Primary Efficacy Endpoint. Understanding that 24-hr ABP may be considered a more standard clinical measure of BP outcome, a powered Secondary Efficacy Endpoint evaluating the reduction in ambulatory 24-hr systolic ABP will also be evaluated. Following the failure of the Symplicity HTN-3 study to demonstrate effectiveness, the use of ABP to evaluate the effect of renal denervation on blood pressure became standard and now at least two studies have demonstrated that ABP can be used to successfully reduce the placebo effect and variability previously associated with the use of office BP. Office BP however has historically been the standard by which antihypertensive medication effectiveness has been assessed and is most commonly used in primary practice to diagnose hypertension. Recent studies indicate that it is possible to closely mimic the BP values recorded with home or ambulatory BP device when using standardized office BP data collection criteria and so seated measures of office BP have been included in RADIANCE II including a powered Secondary Endpoint evaluating the reduction in office systolic BP at 2 months.

5.7. *Justification for Efficacy Performance Criteria*

Incremental reductions in BP are known to decrease the incidence of major cardiovascular events. Reducing systolic BP by as little as 5 mmHg has been shown to be associated with a 14% reduction in the incidence of stroke, a 9% reduction in the incidence of cardiovascular disease and a 7% reduction in mortality.[xxxiv] Furthermore, precedence from pharmaceutical evaluations of antihypertensive medication[xxxv]and from the recently presented DENERHTN[xxxii,] Symplicity Flex[xxxvi] and Symplicity Japan[xxxvii] trials support that a 6 mmHg reduction in BP between treatment and placebo or sham, is an achievable and clinically meaningful goal in both drug washout patients and in severely resistant and mildly resistant hypertensive patients.

5.8. *Minimization of Risk*

The initial data from the RADIANCE HTN SOLO cohort demonstrates that the risks associated with the use of the Paradise ultrasound technology are minimal, however, to once again ensure that subjects are not inappropriately exposed to an increased risk of cardiovascular events, stroke and/or renal stenosis, the following measures have been taken:

- Drug discontinuation will occur in line with accepted Institutional guidelines for a subjects' current antihypertensive medication
- Clinical intervention may be required for patients who have clinical adverse events felt to be related to persistent or elevated hypertension as defined by any of the following:
    - Average Home BP ≥ 170 mmHg systolic or ≥ 105 mmHg diastolic and subsequently confirmed by an average office BP ≥ 180 mmHg systolic or ≥ 120 mmHg diastolic. If an in-office blood pressure cannot be obtained due to the COVID-19 public health emergency, the Home BP Diary will be used to confirm the need for clinical intervention. If elevated hypertension is sustained over 3 days, then medication escalation is recommended.
    - Daytime ABP ≥ 170 mmHg systolic or ≥ 105 mmHg diastolic
- Drug discontinuation is limited to a short period of approximately 3 months during which timeframe subjects are a low risk of any CV event off treatment[xxxix]
- Subjects will be provided with a Home BP device and will be instructed to record their average home BP on the 7 consecutive days immediately prior to Baseline, 1, 2, 3, 4, 5, 6 & 12 month FUs
- Subjects will be seen in clinic every 4 weeks throughout the first 6 months of the study and antihypertensive drug therapy may be initiated at any follow-up in the event that high or low BP action is determined to be required (see Section 8.11)
- Subjects will have antihypertensive drug therapy initiated immediately following the 2 month FU if needed (see Section 8.11.1)
- Non-invasive renal imaging (CTA or MRA) will be required for all subjects at baseline and 6 month FU. An additional FU renal CTA or MRA will be performed at 12-months after the procedure only in subjects randomized to Treatment. Non-invasive renal imaging (CTA or MRA) will be required for all cross-over subjects at 12 month FU post cross-over. Additional CTA/MRA imaging may be required if clinically indicated (e.g. increase in blood pressure, consistent with the protocol defined definition of 'High BP Criteria") or based on the required FU imaging study results (e.g. a change in the minimal lumen diameter along the renal artery ≥0.2 mm).

- In order to ensure continued patient safety oversight during the COVID-19 public health emergency, the study protocol has been amended to allow the remote conduct of certain visit assessments which can reasonably be performed remotely.

6. Subject Selection

6.1. *Study Population and Eligibility*

Subjects eligible for antihypertensive drug therapy and following the general indications/contraindications for use of the Paradise Renal Denervation System will be identified from the general subject population by the enrolling center. In addition, subjects must meet all inclusion criteria and none of the exclusion criteria.

6.2. *Inclusion & Exclusion Criteria*

6.2.1. Inclusion Criteria

Male and female subjects who meet all of the following criteria should be given consideration for inclusion in this clinical investigation, provided no exclusion criterion is met:

- Appropriately signed and dated informed consent
- Age ≥18 and ≤75 years at time of consent
- Documented history of hypertension
- Previously or currently prescribed antihypertensive therapy
- Average seated office BP ≥ 140/90 mmHg <180/120 mmHg at Screening Visit (V0) while stable for at least 4 weeks on 0-2 anti-hypertensive medications of different classes*
- Able and willing to comply with all study procedures

Subjects who meet the following criteria will be considered eligible for randomization:

- Documented daytime ABP ≥ 135/85 mmHg and < 170/105 mmHg at Baseline Visit (V1) after 4-week washout/run-in period
- Suitable renal anatomy compatible with the renal denervation procedure and documented by renal CTA or MRA of good quality performed within one year prior to consent (a CTA or MRA will be obtained in patients without a recent (≤1 year) cross-sectional renal imaging) confirmed by renal angiogram in subjects that continue to procedure (see Exclusion Criteria)
- Sinus rhythm at the time of procedure

**Potassium-sparing diuretics such as Amiloride hydrochloride and Triamterene may be prescribed in combination with another diuretic (e.g. a thiazide or loop diuretic) for their potassium conservation properties. In this situation, the diuretic combination is considered as a single class of anti-hypertensive.*

6.2.2. Exclusion Criteria

Subjects who meet any one of the following criteria will be excluded:

- Renal artery anatomy on either side, ineligible for treatment including:
  - Main renal artery diameter < 3 mm or > 8 mm
  - Main renal treatable artery length < 20 mm (may include proximal branching)
  - A single functioning kidney
  - Presence of abnormal kidney tumors
  - Renal artery with aneurysm

  - Pre-existing renal stent or history of renal artery angioplasty
  - Pre-existing aortic stent or history of aortic aneurysm
  - Prior renal denervation procedure
  - Fibromuscular disease of the renal arteries
  - Presence of renal artery stenosis of any origin ≥ 30%
  - Accessory arteries with diameter ≥2mm <3 mm or > 8 mm*
- Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter
- Known, uncorrected causes of secondary hypertension other than sleep apnea
- Evidence of active infection within 7 days of procedure
- Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma HbA1c ≥ 9.0%)
- Documented history of chronic active inflammatory bowel disorders such as Crohn's disease or ulcerative colitis
- eGFR of <40 mL/min/1.73 m^2 (by Modification of Diet in Renal Disease formula)
- Brachial circumference ≥ 42 cm
- Any history of cerebrovascular event (e.g. stroke, transient ischemic event, cerebrovascular accident)
- Any history of severe cardiovascular event (e.g. myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV)
- Documented confirmed episode(s) of stable or unstable angina within 12 months prior to consent
- Documented repeat (>1) hospitalization for hypertensive crisis within the prior 12 months and/or any hospitalization for hypertensive crisis within three (3) months prior to consent
- Prescribed to any standard antihypertensive of cardiovascular medication (e.g. beta blockers) for other chronic conditions (e.g. ischemic heart disease) such that discontinuation might pose serious risk to health in the opinion of the investigator
- Documented history of persistent or permanent atrial tachyarrhythmia
- Active implantable medical device (e.g. ICD or CRT-D; neuromodulator/spinal stimulator; baroreflex stimulator)
- Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea.
- Primary pulmonary hypertension
- Documented contraindication or allergy to contrast medium not amenable to treatment
- Limited life expectancy of < 1 year at the discretion of the Investigator
- Night shift workers
- Any known, unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or for any reason in the opinion of the investigator, would be unlikely or unable to comply with study protocol requirements or whose participation may result in data analysis confounders
- Pregnant, nursing or planning to become pregnant within 12 months post procedure. Negative pregnancy test required documented within a maximum of 7 days prior to procedure for all women of childbearing potential. Documentation of effective contraception is also required for women of childbearing potential
- Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable)

** These inclusion/exclusion criteria may only be finally determined during the active renal angiogram procedure, subjects will therefore only count towards the enrollment ceiling at the time of randomization*

7. Subject Accountability

7.1. *Point of Enrollment*

All subjects will be considered enrolled following the signing of an informed consent. Since full eligibility for the study may not be confirmable without ABP results after 4-weeks and the need for an invasive procedure (it is possible that the renal anatomy eligibility criteria may only be confirmed during the active renal angiogram procedure), enrolled subjects will only count towards the randomization ceiling at the time of randomization.

7.2. *Re-Consent*

Under specific circumstances, a subject that has previously been found to be ineligible for the study during screening ("Screening Failures" – see Section 7.4) may be re-consented (e.g. reduced brachial circumference due to weight loss; clinically driven changes in anti-hypertensive medication resulting in a change in eligibility; changes to diabetes management; withdrawn during screening due to the COVID-19 public health emergency temporary enrollment suspension, etc.). Any subject that is being considered for re-consent must be approved by the Sponsor.

7.3. *Withdrawal*

All subjects included in the RADIANCE II Trial (including those who have withdrawn or been lost to FU) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to an adverse event, the subject will be followed until resolution of that adverse event or it is otherwise deemed that the event can be closed (e.g. a chronic event), whichever is most applicable to the situation.

Limiting the amount of missing data is key to the successful outcome of the study however, subjects may withdraw from the study at any time with, or without reason. Withdrawal will in no way prejudice the subject's access to further treatment. Attempts to contact subjects who are lost to FU will be documented (e.g. phone calls; letter; email). Additional data may not be collected after the point at which a subject has withdrawn from the study. Reasons for withdrawal include but are not limited to:

- Physician discretion
- Subject choice (withdrawal of consent)
- Lost to FU
- Death
- COVID-19 public health emergency

Withdrawal from the study will be documented on the Patient Status form or equivalent.

7.4. *Subject Status and Classification*

The following classifications will be applied to all subjects:

- Screening Failure: A subject who has signed the informed consent but is found to not meet eligibility criteria either through medical file review or other study-dependent procedures

other than the renal angiogram. The original Consent form and screening documentation for these subjects must be maintained in the Center's files. There are no FU requirements for Screening Failures unless in the event of an adverse event that occurred during the process of defining eligibility, in which case the status of the event will be reviewed and documented within four (4) weeks. Exit from the study will be documented on the Study Status form or equivalent.

- Attempt: A subject who signs the informed consent, meets initial eligibility criteria and has any form of anesthesia/analgesia administered for the procedure but are then excluded (e.g. by renal angiogram). All attempt subjects will have Discharge data collected and will be followed for four (4) weeks (28±3 days) post procedure for safety and any adverse events that occur within that period will be collected. Follow-up should be preferably conducted by phone or office visit. Email FU may be acceptable in the event that the subject is provided with a clear list of questions that can easily be answered. Exit from the study will be documented on the Study Status form or equivalent.
- Treatment: A subject who is successfully randomized per the study protocol. These subjects are followed in accordance with the FU schedule. Any subject that has been randomized will count towards the randomization ceiling even in the event that the treatment was not completed per protocol.

The pre-specified statistical analysis will be documented in the Statistical Analysis Plan (SAP).

8. Methods

8.1. *Visit schedule*

Enrollment of subjects will occur at the clinical sites only after the appropriate Local and National study approvals, "Approval to Enroll" documentation from the Sponsor and written informed consent from subjects have been obtained. Table 8.1-1 summarizes the study visit schedule. Table 8.1-2 summarizes the study cross-over visit schedule.

Table 8.1-1: Visit Schedule

Visit	V0	V1	NA	P1	D1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Visit Description	Screening	Baseline Eligibility	Pre-Procedure Testing	Procedure	Discharge	1 Mo FU	2 Mo FU	3 Mo FU	4 Mo FU	5 Mo FU	6 Mo FU	12 Mo FU	24 Mo FU	36 Mo FU	48 Mo FU	60 Mo FU
Visit Window (days)	NA	28±3 post V0		Max 21 days post V1[ǂ]	NA	30±7	60±7	90±7	120±7	150±7	180±7	360±14	720±30	1080±60	1440±60	1800±60
Informed consent	X															
Average Office BP*	X	X			X[$]	X	X	X	X	X	X	X	X	X	X	X
24-hr Ambulatory BP		X≠					X≠†				X≠†	X≠†				
Medical history (or review)	X	X				X†	X†	X†	X†	X†	X†	X†	X†	X†	X†	X†
Physical Examination	X	X				X	X	X	X	X	X	X	X	X	X	X
Medication Review	X	X		X	X	X†	X†	X†	X†	X†	X†	X†	X†	X†	X†	X†
HTN Medication Withdrawal	X	X	X	X∞	X	X	X									
Home BP Review		X				X†	X†	X†	X†	X†	X†	X†				
HTN Therapy Escalation (if needed per BP criteria)							X†	X†	X†	X†						
CTA/MRA€			X**								X μ	X[T] μ				
QoL Questionnaire(s) (EQ-5D-5L)	X	X√					X†				X†	X†				
12-lead ECG			X√				X				X	X				
Urine Chemistry			X√				X				X	X				
Urine for Drug Metabolite		X√					X				X	X				
Blood Chemistry			X√				X				X	X				
Pregnancy Test (where applicable)			X#													
Diagnostic renal angiogram				X												
Randomization				X												
Renal Denervation Procedure				X[T]												
Pain Perception				X	X											
Blinding Index					X		X†				X†	X†				
Adverse Events		X	X	X	X	X†	X†	X†	X†	X†	X†	X†	X†	X†	X†	X†
Device Deficiencies				X												
Protocol Deviations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BP: Blood Pressure; HTN: hypertension; CTA: Computed Tomographic Angiography; MRA; Magnetic Resonance Angiogram;
**Average seated Office BP will be calculated as well as a standing measure unless specified (section 9.3.1)*
$Optional
ǂABP can be repeated in the event of a technical failure or if insufficient or inadequate data is available
∞Antihypertensive medication during the procedure if needed, is permissible (see Section 8.4.3)
***A recent (within 12 months of consent) good quality, renal MRA or CTA is acceptable*
#within a maximum of 7 days prior to procedure. Testing on the day of procedure is permissible
[T] Treated Subjects
√Note: Pre-procedure tests may be completed at any time from the point a subject attends the Screening Visit (V0) up to the Procedure other than collection of urine for drug metabolite which may NOT be collected prior to V1 and will be collected to coincide with the date of the ABP recording. Review of CTA/MRA images by the Sponsor in collaboration with the clinical site is required prior to procedure and if of insufficient quality may need to be repeated. Allow sufficient time for scheduling if required.
€ CTA/MRA may be required at any time, if clinically indicated.
¥ The procedure may not occur later than a maximum of 21 days after the determination of ABP eligibility associated with the V1 visit.
† Assessment may be conducted remotely if COVID-19 public health emergency restrictions prevent data from being collected in-person
µ CTA/MRA (6 months and 12 months) may be conducted up to 90 days post visit window if unable to do assessment per schedule due to COVID-19 public health emergency restrictions

Table 8.1-2 Visit Schedule for Cross-over Patients

Visit	COV1	COP2	COD2	COV2	COV3	COV4	COV5	COV6	COV7	COV8	COV9
Visit Description	Cross-over Baseline Evaluation	Cross-over Procedure	Cross-over Discharge	Cross-over 1 Mo FU	Cross-over 2 Mo FU	Cross-over 6 Mo FU	Cross-over 12 Mo FU	Cross-over 24 Mo FU	Cross-over 36 Mo FU	Cross-over 48 Mo FU	Cross-over 60 Mo FU
Visit Window (days)	NA	Max 21 days post COV1[¥]	NA	30±7 post COP2	60±7 post COP2	180±7 post COP2	360±14 post COP2	720±30 post COP2	1080±60 post COP2	1440±60 post COP2	1800±60 post COP2
Cross over consent	X										
Cross-over eligibility evaluation	X										
Average Office BP	X[$]		X[+]	X	X	X	X	X	X	X	X
24-hour Ambulatory BP	X[*]				X†	X†	X†				
Home BP Review				X†	X†	X†	X†				
Medical history review	X			X†	X†	X†	X†	X†	X†	X†	X†
Physical Examination	X			X	X	X	X	X	X	X	X
Medication Review	X	X	X	X†	X†	X†	X†	X†	X†	X†	X†
CTA/MRA€							X μ				
QoL Questionnaire(s) (EQ-5D-5L)						X†	X†				
12-lead ECG						X	X				
Blood Chemistry	X[$]				X	X	X				
Urine Chemistry	X[$]				X	X	X				
Urine for Drug Metabolite	X^				X	X	X				
Pregnancy Test (where applicable)	X[#]										
Pain Perception		X	X								
Diagnostic renal angiogram		X									
Renal Denervation Procedure		X									
Adverse Events	X	X	X	X†	X†	X†	X†	X†	X†	X†	X†
Device Deficiencies		X									
Protocol Deviations	X	X	X	X	X	X	X	X	X	X	X

BP: Blood Pressure; HTN: hypertension; CTA: Computed Tomographic Angiography; MRA; Magnetic Resonance Angiogram;
+ Optional
**Note: in the event of a technical failure or if insufficient or inadequate data is available following the 24-hr ABP recording to determine eligibility, the subject can be asked to repeat the measurement. There cannot be more than 2 valid ABPM recordings performed within a maximum of 6 weeks to document uncontrolled BP*
$ Results from tests recently performed during study follow-up visits may be used unless there were major changes to the patient condition or treatment. Results must meet protocol baseline eligibility criteria.
^Urine collected for drug adherence at the 12 month study follow-up visit may be used if the 12 month FU is considered the cross-over baseline visit. If not, urine for adherence testing will be collected to coincide with the ABP used to determine cross-over eligibility
 # within a maximum of 7 days prior to procedure
€ CTA/MRA may be required at any time, if clinically indicated.

¥ It is recommended that the cross-over procedure occur within 21 days of the determination of ABP eligibility associated with the baseline COV1 FU visit.
† Assessment may be conducted remotely if COVID-19 public health emergency restrictions prevent data from being collected in-person
µ 12 Month crossover CTA/MRA may be conducted up to 90 days post visit window if unable to do assessment per schedule due to COVID-19 public health emergency restrictions

8.2. *V0: Study Screening Visit*

Subjects who meet general eligibility for consideration for the study will sign an informed consent. All subjects will have their seated average office BP measured (see Section 9.1), a medical history, physical exam and full review of current medication (including antihypertensive medications; non-cardiovascular medications; supplements etc.). Subjects with an average office BP ≥ 140/90 mmHg < 180/120 mmHg currently prescribed to antihypertensive medication will be asked to stop taking all antihypertensive medication for the 4-week washout period (follow Institutional guidelines for medication washout). All eligible subjects will be asked to complete Quality of Life questionnaires (including at a minimum, the EQ-5D-5L). Subjects not currently taking their prescribed anti-hypertensive medication, will be asked to stay medication-free for a 4-week run-in period. All subjects starting the washout/run-in period, will be provided with a Home BP device and trained on its use (section 9.3.2). Subjects who fail to meet any inclusion criteria and/or are determined to have met any exclusion criteria at this visit will be classified as "Screening Failures" (see Section 7.4).

Table 8.2-1: Data to be collected during the screening visit (V0)

Data Collection	Location of Source
Informed Consent	Maintain original at site. Provide a copy to the subject
Average seated office BP Measurement per guidelines (including standing BP)	Maintain at site
Medical history and physical examination including but not limited to prior history of antihypertensive therapy, sex, race; age at consent, height, weight, brachial circumference, abdominal circumference; relevant cardiovascular history; heart rate	Maintain at site
QoL Questionnaire(s) (EQ-5D-5L)	Maintain at site
Renal CTA/MRA Review (if available)	Upload copy to BioClinica
All current medication (hypertensive and non-hypertensive including supplements etc.)	Maintain at site
Protocol Deviations	Maintain at site

8.3. *V1: Baseline Eligibility Visit*

All subjects will return to the clinical center to have their office BP measured 4 weeks (28±3 days) after either the discontinuation of their hypertensive medication or the beginning of their run-in period. Subjects will record their Home BP (section 9.3.2) for the 7 consecutive days prior to the visit and will be asked to bring their Home BP device and Diary with them to the visit. The investigational center should contact the subject to remind them when to start their home BP recordings and to bring their Home BP device and Diary to the FU.

Clinic visits will occur in the morning. It is strongly recommended that the V1 visit occur between 08:00 and 10:00am. The approximate time of the visit will be documented. In the event that the visit does not occur in the morning, the same visit time will be repeated for all subsequent visits where blood pressure is measured.

All subjects will have a seated office BP measurement recorded (section 9.3.1). Subjects whose BP does not meet the Safety Escape Criteria (section 8.11.2), will undergo a 24-hr

ABP measurement (following training on how to use the ABP device). Subjects will be requested to return the ABP device the following day. Since this ABP data marks the point of eligibility for the study, the subject is requested to return to the clinical center with the ABP device.

All eligible subjects will be asked to complete the QoL questionnaire(s), at minimum the EQ-5D-5L, and to provide a urine sample for detection of antihypertensive drugs. The urine sample for detection of antihypertensive drugs will be collected to coincide with the date of initiation of the baseline ABP but not to exceed 24 hours after initiation. Table 8.3-1 documents the data to be collected during the baseline visit.

Table 8.3-1: Data to be collected during the Baseline Eligibility Visit (V1)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing BP)	Maintain at site
Medical history review	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Changes in current medication (hypertensive and non-hypertensive)	Maintain at site
Home BP Diary Review	Maintain at site
QoL Questionnaire(s) (EQ-5D-5L)	Maintain at site
Urine for antihypertensive drug screening[$]	Freeze sample at site
Documentation of any adverse events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site
[$]*To be collected to coincide with the date of the baseline ABP*	

8.3.1. Baseline ABP Review and Final Eligibility Testing

Subjects whose baseline, daytime ABP is documented to be ≥135/85 mmHg and <170/105 mmHg will be considered eligible for the study. Additional testing is required prior to procedure (See section 8.3.2).

Table 8.3-2: Data to be collected during ABP Review

Data Collection	Location of Source
24-hr ABP report*	Upload to core lab. Maintain copy of report at site
Documentation of any adverse events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

**Note: in the event of a technical failure or if insufficient or inadequate data is available following the 24-hr ABP recording to determine eligibility, the subject can be asked to repeat the measurement. Contact the Sponsor prior to repeating to ensure a repeat ABP is appropriate. In the event of a repeat ABP, a new urine sample for detection of antihypertensive medication will be collected to coincide with the date of the new ABP. It is also recommended that office BP measurements be repeated.*

Subjects who do not meet the protocol-defined ABP criteria will be classified as "Screening Failures" (See section 7.4). These subjects may then return to standard of care.

8.3.2. Additional Pre-Procedure Testing

Once the ABP eligibility has been confirmed, there are a number of additional tests that are required to be completed prior to the Procedure. Where applicable, these tests may be completed pre-emptively as part of the earlier visits or completed during the visit when the subject returns to the hospital with their ABP device or may be scheduled separately at any time post V0.

Table 8.3-3: Testing to be completed prior to Procedure

Data Collection	Location of Source
Screening renal CTA or MRA to evaluate renal anatomy (a recent CTA or MRA within 12 months of consent is acceptable). Requires review by Sponsor prior to Procedure	Upload copy to BioClinica
Baseline 12-lead ECG	Maintain at site
Baseline urine (for chemistry)	Maintain report at site
Baseline Blood (for chemistry)	Maintain report at site
Negative Pregnancy test (within 7 days of procedure if applicable)	Maintain at site

The screening CTA/MRA will need to be evaluated by, at a minimum, a designated Sponsor representative in collaboration with the clinical site. Images that do not meet minimum requirements may need to be repeated. For this reason, the CTA/MRA should be scheduled to allow sufficient time for review and if needed, repeat. In the event the screening CTA or MRA documents evidence of ineligible renal artery anatomy or any other exclusion criteria, the subject will not be eligible for the procedure and will be classified as a "screening failure" (see section 7.4). These subjects may return to standard of care.

8.4. *P1. Hospitalization for Renal Denervation or Blinded (Sham) Procedure*

Once a subject has met all the screening criteria for the study including diagnostic CTA or MRA, they will be scheduled for the renal angiogram and renal denervation procedure. The procedure may not occur later than a maximum of 21 days after the determination of ABP eligibility associated with the V1 visit. In the event a procedure cannot be scheduled within that time frame the Sponsor must be notified. Subjects of childbearing potential must have a documented negative pregnancy test dated within a maximum of 7 days prior to the procedure. Pregnancy tests completed immediately prior to procedure are permissible.

8.4.1. Blinding Process

No study personnel who will be responsible for recording patient ABP or OBP during FU visits, post discharge, may be present at the point of randomization which occurs after the completion of the diagnostic renal angiogram. All patients will be sedated prior to randomization. In addition, the use of headphones and eye covers is required for any subjects that are not under general anesthesia. A procedure script will be provided in the event a subject is randomized to "Control".

8.4.2. Procedural Pain Perception

All subjects will be asked to complete a Pain Numeric Rating Scale prior to the procedure to document their level and (if applicable), location of pre-existing pain. This will be repeated prior to hospital discharge.

Reports of pain should be recorded in the case report form as an adverse event, and the investigator should use their judgement to assess relationship to procedure and/or investigational device.

8.4.3. Hypertensive Medications Pre-Procedure

All changes in antihypertensive medication since the V0 visit will be documented. This does not include any transient changes that occur specifically for the procedure. The use of temporary pharmacologic intervention for control of blood pressure prior to and during the peri-procedural phase in order to minimize the risks of puncture site hematoma, is permissible per physician discretion.

8.4.4. Procedural Medications

Appropriate systemic anti-coagulation shall be administered prior and/or during treatment to minimize the risk of thrombus formation. The risks of using the Paradise System in patients who cannot be anti-coagulated are unknown. The same anticoagulation procedures should be observed for all patients. The clinician can consider the use of low dose prophylactic aspirin if recommended by local clinical practice.

Understanding that there is evidence that the renal denervation treatment may be associated with pain, appropriate analgesic/anxiolytic medication to ensure subject comfort and to maintain blinding is required. Medications such as Morphine sulphate, Fentanyl and Midazolam are recommended and should be administered as per local policy. The use of intra-arterial vasodilators for prevention or treatment of renal artery spasm is per physician discretion. It is recognized that this procedure may require a deeper level of sedation than for standard percutaneous procedures. Accordingly, investigators should ensure that appropriate post-procedural monitoring is in place for subjects, particularly taking into account that the population may be elderly and hypertensive. Monitoring should be per institutional guidelines.

8.4.5. Diagnostic Renal Angiogram (all subjects)

All subjects will undergo a diagnostic, renal angiogram which should be per Institutional practice via femoral artery access. The Paradise System requires the use of a guide catheter of minimum diameter 0.081", typically 7 French. It is recommended, however, that investigators use a smaller size access sheath (e.g. 4 or 5 French) to perform the diagnostic angiogram consistent with standard institutional practice; and that for those patients randomized to renal denervation, the sheath be exchanged for a larger one to accommodate the Paradise System.

Treatment is required to be bilateral. Angiographic evidence of any of the following criteria on either side, would deem the subject as ineligible for randomization. In the event that additional imaging techniques are used such as Intravascular Ultrasound ("IVUS") its use must be documented:

- Main renal artery diameter < 3 mm or > 8 mm
- Main renal treatable artery length< 20 mm
    - A minimum of 20mm treatable length will allow for delivery of at least two emissions in each renal artery. Treatable length may include artery branches (artery length is best determined by CTA/MRA)

- A single functioning kidney
- Presence of abnormal kidney tumors
- Renal artery with aneurysm
- Pre-existing renal stent or history of renal artery angioplasty
- Pre-existing aortic stent or history of aortic aneurysm
- Prior renal denervation procedure
- Fibromuscular disease of the renal arteries
- Presence of renal artery stenosis of any origin ≥ 30%
- Accessory arteries with diameter ≥ 2mm <3 mm or > 8 mm

In the event that all these angiographic criteria cannot be confirmed with a global angiogram, a selective renal angiogram may be conducted. Renal artery measurements made during the angiogram will be documented. Measurements made during the renal angiogram are considered the final decision point for renal anatomy eligibility (renal artery length, however is best measured via a 'snake' view in CTA/MRA rather than renal angiogram).

8.4.6. Randomization

Randomization will occur following the diagnostic renal angiogram. Only randomized patients will count towards the randomization ceiling. All randomized subjects will be followed per protocol, even in the event that treatment cannot be delivered in accordance with the protocol.

8.4.7. Blinded (Sham) Procedure

For the control patients, the diagnostic renal angiogram will be considered the sham procedure.

8.4.8. Renal Denervation Procedure

Specific details of the renal denervation procedure will be provided in the "Instructions For Use". Briefly, using standard interventional technique, gain access to the femoral artery and place a guide catheter compatible with the Paradise System (0.081" minimum inner diameter). Carefully advance the guide catheter into the left or right renal artery using fluoroscopic guidance. Verify patency by performing an angiogram and measure and record the distal mid and proximal artery diameters in order to select the appropriate Paradise catheter balloon size (see Table 8.4-1). Select the Paradise Catheter based on the smallest measured diameter of the artery and follow these steps to deliver treatment bilaterally:

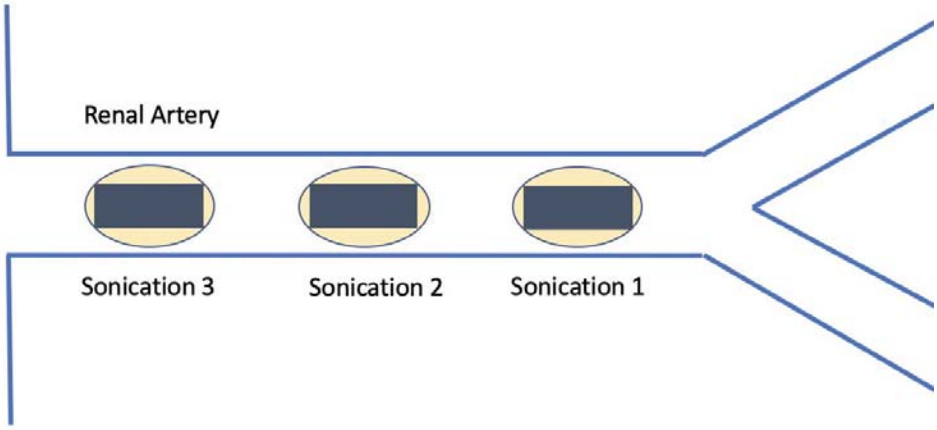
Table 8.4-1: Paradise Catheter Range

Artery Diameter Range	Catheter Reference	Balloon diameter
3 to <3.5mm	PRDS-063-02	3.5 mm
3.5 to <4.2mm	PRDS-064-02	4.2 mm
4.2 to <5 mm	PRDS-065-02	5 mm
5 to <6 mm	PRDS-066-02	6 mm
6 to <7 mm	PRDS-067-02	7 mm
7 to ≤8 mm	PRDS-068-02	8 mm

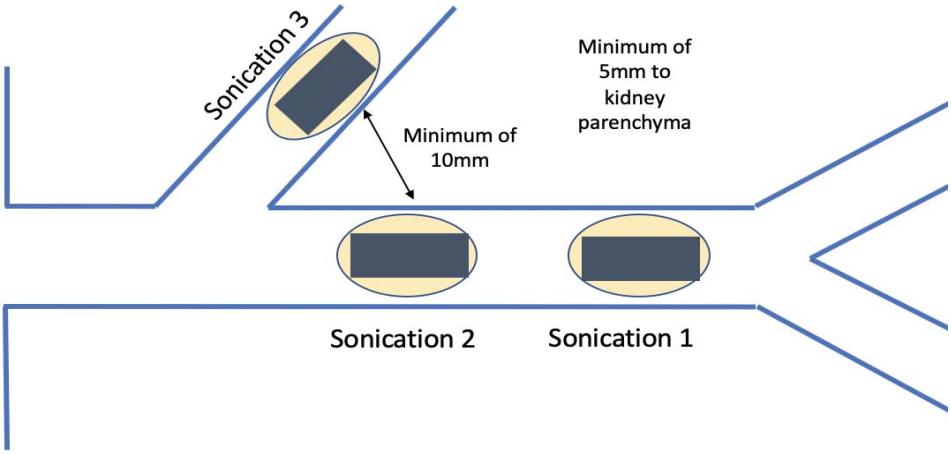
- Prepare and attach the Paradise Cartridge, Paradise Connection Cable, and sterile water supply as per the Instructions for Use
- Using sterile technique, open the Paradise Catheter package and carefully remove the device.
- Connect the Paradise Cartridge extension tubing to the fluid luer connections of the Paradise Catheter. The order of connections does not matter
- Prepare the Paradise Catheter according to the Instructions for Use
- Flush the center lumen of the Paradise Catheter prior to tracking over a wire
- Remove access devices from lumen of guide catheter and insert a 0.014" guidewire
- Verify the balloon on the Paradise Catheter is deflated. If balloon is not deflated, press the DEFLATE button on the Paradise Generator touch screen to deflate the balloon
- Track the Paradise Catheter over the 0.014" guidewire and gently insert the Paradise Catheter into the "Bleedback" hemostasis valve and guide catheter
- Advance the Paradise Catheter into the renal artery
- See the Instructions for Use for balloon inflation, sonication, and balloon deflation instructions
- Treatment Strategy
    - Deliver a minimum of two sonications each in the left and right renal arteries (see Figure 8.4-1 for an example treatment strategy).
        - The first sonication should be delivered at a distance of *at least* 5 mm, or one (1) radiopaque transducer length, from the artery bifurcation
        - Additional sonications should be delivered in a non-overlapping configuration, with each subsequent sonication delivered proximal to the prior sonication. Note: Do not place sonication over the ostium of a branch vessel
        - If proximal artery branching, and diameter of branch is ≥ 3 mm, one (1) sonication should be delivered in the branch in a location at least 5 mm from the kidney parenchyma, and at least 10mm from adjacent sonications
        - If proximal bifurcating branches (≥ 3 mm diameter) in short main renal arteries, a minimum of one (1) sonication should be delivered in each branch in a location at least 5 mm from the kidney parenchyma, and at least 10 mm from adjacent sonications
        - Maintain a gap of ≥ 5 mm, or at least one (1) radiopaque transducer length between the final sonication and the renal artery/aorta ostium
    - If an accessory artery/side branch is present and has a diameter ≥ 3 mm, one (1) sonication should be delivered
- When treatment in either the left or right artery is completed, withdraw the Paradise Catheter back into the guide catheter
- Position the guidewire and guiding catheter into the non-treated artery and repeat procedure
- Remove the Paradise Catheter, guidewire and guide catheter after treatment of both arteries.
- Close the wound per standard Institutional practice taking into consideration the size of the guide catheter(s) used. Follow standard-of-care post-intervention monitoring procedures including pain control, post sedation monitoring and FU

Figure 8.4-1: Examples of Treatment Strategy in Renal Artery, Accessory Artery, and Proximal Side Branches

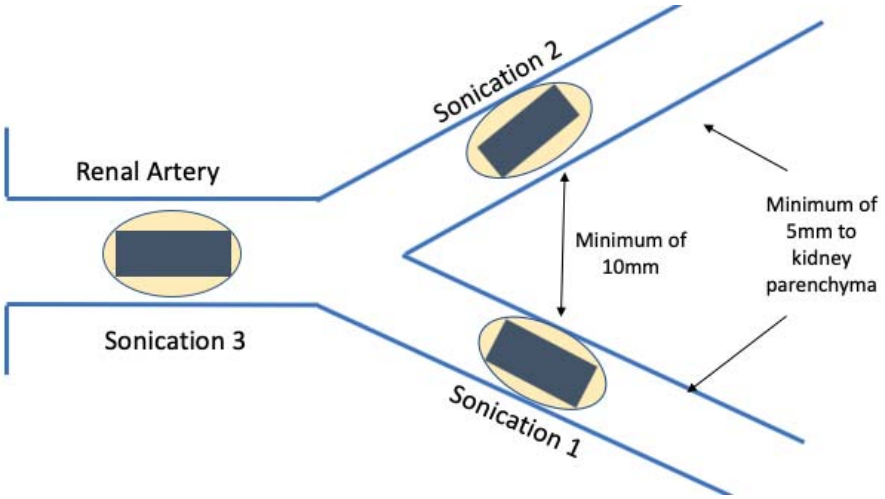
8.4-1a: Three ultrasound sonications in main renal artery



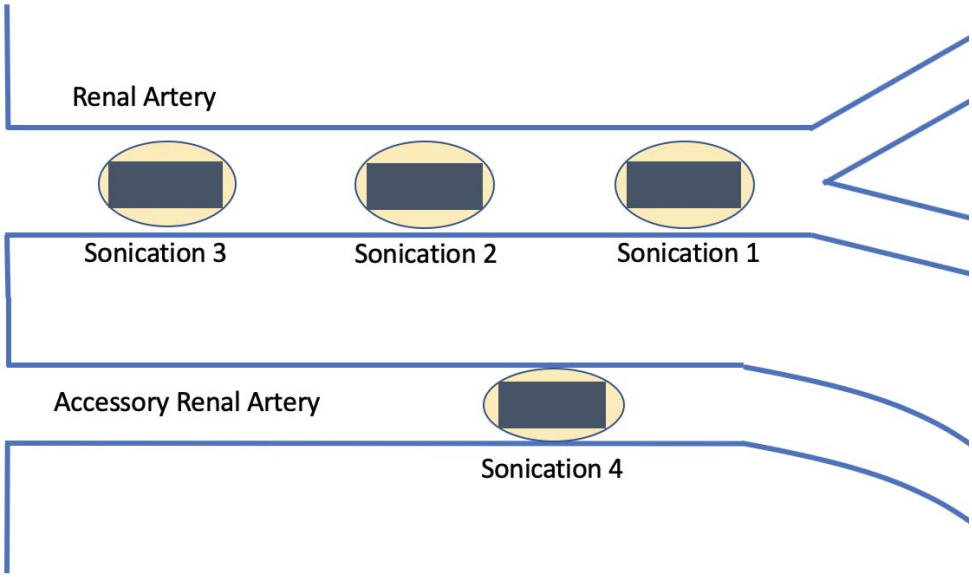
8.4-1b: Two ultrasound sonications in main renal artery and one in proximal side branch artery



8.4-1c: One ultrasound sonication in main renal artery and one in proximal bifurcating branches



8.4-1d: Three ultrasound sonications in main renal artery and one in accessory renal artery



8.4.9. Data Collection

Table 8.4-2 documents the data to be collected during the renal denervation or control (sham) procedure. In the event of a device deficiency or adverse event attributable or potentially attributable to the Paradise System (see Section 11.0; Safety Reporting), the Paradise catheter and any associated accessories will be returned to the Sponsor for further investigation. All used devices must be disposed of appropriately. Unused devices will be returned to the Sponsor at the end of the trial or in the event the Investigational Site is closed prior to end of trial.

Table 8.4-2: Data to be collected during the Procedure (P1)

Data Collection	Location of Source
Pain Numeric Rating Scale (prior to procedure)	Maintain at site
Procedure times (femoral access to femoral closure)	Maintain at site
Procedural Medication (anesthesia; analgesia; anticoagulation if used; contrast volume; radiation dose etc.)	Maintain at site
Procedural angiogram including renal anatomy measurements (global or selective)	Upload copy to BioClinica. Maintain copy of report at site
Randomization	CRF or equivalent
Treated Subjects: Device and generator data including all accessories (guide catheters; guide wires)	Maintain at site
Treated Subjects: Paradise catheter usage; ultrasound ablation detail	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Device Deficiencies	Upload copy to BioClinica as requested
Device Disposition (Catheters; cartridges; cables)	Maintain at site
Protocol Deviations	Maintain at site

8.5. *D1. Hospital Discharge*

Subjects will be discharged from the hospital according to institutional process. It is recommended that personnel un-blinded to the subjects' randomization conduct the Discharge Visit. If blinded personnel conduct the Discharge, they should understand the device and procedure and be aware of potential adverse events related to both. The repeat Pain Numeric Rating Scale and blinding index will be collected prior to hospital discharge. Table 8.5-1 documents the data to be collected prior to discharge from the hospital.

Table 8.5-1: Data to be collected prior to Discharge (D1)

Data Collection	Location of Source
Average seated office BP (optional)	Maintain at site
Pain Numeric Rating Scale	Maintain at site
Blinding Index	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

Following discharge from the hospital, subjects will be required to remain free of hypertensive medication at least through the 2-month FU visit, unless in the event of a BP emergency or other clinical events that require a change of medication (see Section 8.11.2). Ensure that the subject is aware that *ANY* changes in hypertensive medications must be reported.

8.6. *In Clinic Follow-up Visits*

Other than for reasons related to the COVID-19 public health emergency (see below), subjects will be required to return to their investigational clinical center for FU 1, 2, 3, 4, 5, 6, 12, 24, 36, 48 & 60 months post-procedure date. Whenever possible, study assessments will be made by the same designated member of the study team.

Clinic visits will be in the morning. It is strongly recommended that clinic visits be scheduled between 08:00 and 10:00am. In the event that it is not possible to schedule a morning appointment, every attempt should be made to ensure that FUs occur at the same time. This is particularly important for FUs where ABP data is collected to ensure that the ABP recording is started at approximately the same time (appointment times will be collected).

Home BP measurements will be taken for the 7 consecutive days immediately prior to the 1, 2, 3, 4, 5, 6 & 12 month FU. The subject is requested to bring their Home BP device and Diary to these FUs for review. The investigational center should contact the subject to remind them when to start their Home BP recordings and to bring their Home BP device & Diary to the FU.

An 8-hour overnight fast is required prior to any FU visits where blood will be taken (2, 6 & 12 months). Subjects taking anti-hypertensive medication during their participation in the trial will be asked to bring their morning dose of anti-hypertensive medication with them to their FU rather than take it in the morning. They will be observed taking their anti-hypertensive medication as part of the FU. The investigational center should contact the subject prior to each visit to remind them of the need for overnight fasting and to bring their morning hypertensive medication to the FU if applicable (See Section 8.11).

In the event that a scheduled in-clinic visit is not possible due to the COVID-19 public health emergency, the follow-up visit may be conducted remotely (e.g. by phone or video teleconference) as feasible. Visit assessments may be conducted remotely as detailed in the Visit Schedule (See Table 8.1-1) and as described below. These circumstances must be documented and will be considered protocol deviations for COVID-related tracking purposes. All other assessments not described below must be conducted in-person or documented as protocol deviations if they are not completed. Any data collected remotely will be documented in the EDC as such.

Testing and/or assessments that may be performed remotely due to COVID-19 public health emergency include:

- Remote placement of 24-hour ambulatory blood pressure monitor (ABPM), under guidance of the site personnel (instruction using video conferencing or equivalent is strongly recommended);
- Medical history review;
- Weight and abdominal circumference may be self-reported if subject has proper measurement tools (i.e. scale and measuring tape) and performed under guidance of research coordinator via video conferencing or equivalent;
- Medication review;
- Home BP review;
- Antihypertensive medication escalation, as per the guidelines in Section 8.11.1, may be initiated based upon the home blood pressure diary; confirmation by office or ABP measurements will not be required;
- Quality of Life Questionnaire (EQ-5D-5L) may be conducted over the phone using the validated phone interviewer survey;
- CTA/MRA may be conducted up to 90 days beyond the end of the visit window;
- Blinding index;
- Adverse event assessment.

8.6.1. V2: One month Visit (30±7 days post procedure)

Subjects will be required to return to their investigational clinical center one (1) month post procedure. Table 8.6-1 documents the data to be collected.

Table 8.6-1: Testing to be collected at one month visit (V2)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical history review	Maintain at site
Home BP Diary Review	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

8.6.2. V3: Two Month Primary Efficacy Endpoint Visit (60±7 days post procedure)

Subjects will be required to return to their investigational clinical center two (2) months post procedure. The two-month visit marks the timing of the Primary Efficacy endpoint data collection but patients will remain blinded through to the 12-month FU visit. Changes in hypertension medication are permissible following the two-month visit as described in Section 8.11.1. All subjects will have urine collected prior to the restart of any antihypertensive medication to check for compliance. In the event that a subject is eligible to restart on antihypertensive medication, ensure that the 2 Month ABP recording is initiated prior to the restart. Table 8.6-2 documents the data to be collected.

Table 8.6-2: Testing to be collected at two month visit (V3)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical history review	Maintain at site
Home BP Diary Review	Maintain at site
24-hr ABP report*	Upload to core lab. Maintain copy of report at site
QoL Questionnaire(s) (EQ-5D-5L)	Maintain at site
Urine for drug metabolite[$]	Freeze sample at site
Urine (for chemistry)	Maintain at site
Blood (for chemistry)	Maintain at site
12-lead ECG	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Changes in medication	Maintain at site
Blinding Index	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site
[$]*To be collected to coincide with the date of the 2 Month ABP*	

**Note: in the event of a technical failure or if insufficient or inadequate data is available following the 24-hr ABP recording to determine eligibility, the subject can be asked to repeat the measurement. Contact the Sponsor prior to repeating to ensure a repeat ABP is appropriate. In the event of a repeat ABP, a new urine sample for detection of antihypertensive medication will be collected to coincide with the initiation date of the new ABP but not to exceed 24 hours after initiation. It is also recommended that office BP measurements be repeated.*

8.6.3. V4: Three Month Visit (90±7 days post procedure)

Subjects will be required to return to their investigational clinical center three (3) months post procedure. Table 8.6-3 documents the data to be collected.

Table 8.6-3: Testing to be collected at three month visit (V4)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical history review	Maintain at site
Home BP Diary Review	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

8.6.4. V5: Four Month Visit (120±7 days post procedure)

Subjects will be required to return to the clinical center four (4) months post procedure. Table 8.6-4 documents the data to be collected.

Table 8.6-4: Testing to be collected at four month visit (V5)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical history review	Maintain at site
Home BP Diary Review	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

8.6.5. V6: Five Month Visit (150±7 days post procedure)

Subjects will be required to return to the clinical center five (5) months post procedure. Table 8.6-5 documents the data to be collected.

Table 8.6-5: Testing to be collected at five month visit (V6)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical history review	Maintain at site
Home BP Diary Review	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

8.6.6. V7: Six Month Visit (180±7 days post procedure)

Subjects will be required to return to the clinical center six (6) months post procedure. All subjects will have urine collected prior to any changes in antihypertensive medication to check for compliance at the end of the period of pre-defined escalation. The six-month visit marks the time when anti-hypertensive medication changes can be made per the discretion of the investigator after this visit. Ensure that the 6 Month ABP recording is initiated prior to any changes in anti-hypertensive medication. Table 8.6-6 documents the data to be collected.

Table 8.6-6: Testing to be collected at six month visit (V7)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical history review	Maintain at site
Home BP Diary Review	Maintain at site
24-hr ABP report*	Upload to core lab. Maintain copy of report at site
QoL Questionnaire(s) (EQ-5D-5L)	Maintain at site
Urine for drug metabolite$	Freeze sample at site
Urine (for chemistry)	Maintain at site
Blood (for chemistry)	Maintain at site
12-lead ECG	Maintain at site
Renal CTA/MRA	Upload copy to BioClinica. Maintain copy of report at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Blinding Index	Maintain at Site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site
$To be collected to coincide with the date of the 6 Month ABP	

**Note: in the event of a technical failure or if insufficient or inadequate data is available following the 24-hr ABP recording to determine eligibility, the subject can be asked to repeat the measurement. Contact the Sponsor to ensure a repeat ABP is appropriate. In the event of a repeat ABP, a new urine sample for detection of antihypertensive medication will be collected to coincide with the initiation date of the new ABP but not to exceed 24 hours after initiation. It is also recommended that office BP measurements be repeated.*

8.6.7. V8: Twelve Month Visit (360±14 days post procedure)

Subjects will be required to return to the clinical center twelve (12) months post procedure. The 12 month visit marks the end of the period of blinding for all subjects. Unblinding of the subject will be done once the 12 Month ABP recording has been completed. All subjects will have urine collected to document compliance to any antihypertensive medications. Ensure that the 12 Month ABP recording is initiated prior to any changes in anti-hypertensive medication. Table 8.6-7 documents the data to be collected.

Table 8.6-7: Testing to be collected at twelve month visit (V8)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical history review	Maintain at site
Home BP Diary Review	Maintain at site
24-hr ABP report*	Upload to core lab. Maintain copy of report at site
Renal CTA/MRA (Treated Subjects only)	Upload copy to BioClinica. Maintain copy of report at site
QoL Questionnaire(s) (EQ-5D-5L)	Maintain at site
Urine for Drug Metabolite[$]	Freeze sample at site
Urine (for chemistry)	Maintain at site
Blood (for chemistry)	Maintain at site
12-lead ECG	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Blinding Index	Maintain at Site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to Bioclinica as requested
Protocol Deviations	Maintain at site
[$]To be collected to coincide with the date of the 12 Month ABP	

**Note: in the event of a technical failure or if insufficient or inadequate data is available following the 24-hr ABP recording to determine eligibility, the subject can be asked to repeat the measurement. Contact the Sponsor to ensure a repeat ABP is appropriate. In the event of a repeat ABP, a new urine sample for detection of antihypertensive medication will be collected to coincide with the initiation date of the new ABP but not to exceed 24 hours after initiation. It is also recommended that office BP measurements be repeated.*

8.6.8. V9, V10, V11 & V12: 24, 36, 48 & 60 Month Visits

Subjects will be required to return to the clinical center at twenty-four (24), thirty-six (36), forty-eight (48) & sixty (60) months post procedure. Table 8.6-8 documents the data to be collected.

Table 8.6-8: Testing to be collected at 24, 36, 48 & 60 Month visits (V9, V10, V11, V12)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical history review	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

8.7. *Cross-Over Data Collection*

A cross-over baseline visit is required to collect current medication, office and ambulatory BP data for subjects that elect to cross-over. Subjects with an average daytime ambulatory systolic BP ≥ 135 mmHg and/or diastolic BP ≥ 85mmHg at their cross-over baseline visit will be eligible for cross-over. The cross-over procedure should be scheduled within 21 days of the valid, eligible, cross-over baseline ambulatory BP. In the event it is not possible to meet the 21 day criteria, contact the Sponsor for guidance on whether the baseline ABPM and or additional pre-procedure testing needs to be repeated.

In the event that the subject remains uncontrolled at their 12-month FU and cross-over has been authorized, data from the 12 month FU (V8) may be used for the baseline (COV1) visit. This is also acceptable if the subject has reached any other scheduled FU post 12-months at the time they elect to cross-over. Data to be collected at the cross-over baseline visit is shown in Table 8.7-1.

In the event that a scheduled cross-over follow-up in-clinic visit is not possible due to the COVID-19 public health emergency, the follow-up visit may be conducted remotely (e.g. by phone or video teleconference) as feasible. Visit assessments may be conducted remotely as detailed in the Crossover Visit Schedule (Table 8.1-2) and as described below. These circumstances must be documented and will be considered protocol deviations for COVID-related tracking purposes. All other assessments not described below must be conducted in-person or documented as protocol deviations if they are not completed.

Testing and/or assessments that may be performed remotely due to COVID-19 include:

- Remote placement of 24-hour ambulatory blood pressure monitor (ABPM), under guidance of the site personnel (instruction using video conferencing or equivalent is strongly recommended);
- Medical history review;

- Weight and abdominal circumference may be self-reported if subject has proper measurement tools (i.e. scale and measuring tape) and performed under guidance of research coordinator via video conferencing or equivalent;
- Medication review;
- Home BP review;
- Quality of Life Questionnaire (EQ-5D-5L) may be conducted over the phone using the validated phone interviewer survey;
- CTA/MRA may be conducted up to 90 days beyond the end of the visit window;
- Adverse event assessment.

Table 8.7-1: Data to be collected at Cross-over Baseline (COV1)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP) [$]	Maintain at site
Medical History Review	Maintain at site
24-hr ABP report*[$]	Upload to core lab. Maintain copy of report at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate[$]	Maintain at site
Current medications	Maintain at site
Urine for Drug Metabolite [$]	Freeze sample at site
Baseline Blood (for chemistry)[$]	Maintain at site
Baseline Urine (for chemistry)[$]	Maintain at site
Negative Pregnancy test (within 7 days of procedure, if applicable)	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

**Note: in the event of a technical failure or if insufficient or inadequate data is available following the 24-hr ABP recording to determine eligibility, the subject can be asked to repeat the measurement. Contact the Sponsor to ensure a repeat ABP is appropriate. There cannot be more than 2 valid ABPM recordings performed within a maximum of 6 weeks to document uncontrolled BP. In the event of a repeat ABP, a new urine sample for detection of antihypertensive medication will be collected to coincide with the initiation date of the new ABP but not to exceed 24 hours after initiation. It is also recommended that office BP measurements be repeated.*

[$]Results from tests recently performed during study follow-up visits may be used unless there were major changes to the patient condition or treatment. Results must meet protocol baseline eligibility criteria. The date of collection of urine for antihypertensive medication testing will coincide with the initiation date of the ABP used to determine eligibility but not to exceed 24 hours after initiation.

It is recommended that the cross-over procedure occur within 21 days of the determination of ABP eligibility associated with the baseline COV1 FU visit. In the event it is not possible to meet the 21 day criteria, contact the Sponsor for guidance on whether the ABPM and/or additional pre-procedure testing needs to be repeated. The cross-over procedure should be conducted according to the detail in Section 8.4.8. The data to be collected during Cross-Over Treatment procedures is shown in Table 8.7-2.

Table 8.7-2: Data to be collected during the Cross-Over Procedure (COP2)

Data Collection	Location of Source
Pain Numeric Rating Scale (prior to cross-over procedure)	Maintain at site
Procedure times (femoral access to femoral closure)	Maintain at site
Procedural Medication (anesthesia; analgesia; anticoagulation if used; contrast volume; radiation dose etc.)	Maintain at site
Procedural angiogram including renal anatomy measurements (global or selective)	Upload copy to BioClinica. Maintain copy of report at site
Device and generator data including all accessories (guide catheters; guide wires)	Maintain at site
Paradise catheter usage; ultrasound ablation detail	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Device Deficiencies	Maintain at site
Device Disposition (Catheters; cartridges; cables)	Maintain at site
Protocol Deviations	Maintain at site

Hospital discharge should be conducted according to the detail in Section 8.5 other than the need for Blinding Index. Table 8.7-3 documents the data to be collected prior to discharge from the hospital for cross-over subjects.

Table 8.7-3: Data to be collected prior to Cross-over Discharge (COD2)

Data Collection	Location of Source
Average seated office BP Measurement (optional)	Maintain at site
Medication Review	Maintain at site
Pain Numeric Rating Scale	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

Subjects will be required to return to their investigational clinical center one (1) month post procedure. Table 8.7-4 documents the data to be collected.

Table 8.7-4: Data to be collected at 1 Month Cross-over FU (COV2)

Data Collection	Location of Source
Home BP Diary Review	Maintain at site
Average seated office BP Measurement per guidelines	Maintain at site
Medical History Review	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Medication Review	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica if requested
Protocol Deviations	Maintain at site

Ambulatory and office BP measurements will be recorded at the 2, 6 and 12 month FUs for all cross-over subjects. Non-invasive imaging (renal CTA/MRA) will also be required for all subjects at the 12 month FU visit. Table 8.7-5 documents the data to be collected at FU.

Table 8.7-5: Data to be collected at 2, 6 & 12 Month Cross-over FUs (COV3, COV4, COV5)

Data Collection	Location of Source
Home BP Diary Review	Maintain at site
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical History Review	Maintain at site
24-hr ABP report*	Upload to core lab. Maintain copy of report at site
12-lead ECG (6 Month & 12 Month only)	Maintain at site
Medication Review	Maintain at site
QoL Questionnaire(s) (EQ-5D-5L) (6 Month & 12 Month only)	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Renal CTA/MRA (12 Month FU Only)	Upload copy to BioClinica. Maintain copy of report at site
Changes in medication	Maintain at site
Blood (for chemistry)	Maintain at site
Urine (for chemistry)	Maintain at site
Urine for Drug Metabolite[$]	Freeze sample at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site
[$]To be collected to coincide with the date of the Cross-over 2-Month, 6-Month and 12-Month ABP	

**Note: in the event of a technical failure or if insufficient or inadequate data is available following the 24-hr ABP recording to determine eligibility, the subject can be asked to repeat the measurement. Contact the Sponsor to ensure a repeat ABP is appropriate. In the event of a repeat ABP, a new urine sample for detection of antihypertensive medication will be collected to coincide with the initiation date of the new ABP but not to exceed 24 hours after initiation. It is also recommended that office BP measurements be repeated.*

Office BP measurements will be recorded at the 24, 36, 48 & 60 month FU for all cross-over subjects. Table 8.7-6 documents the data to be collected at FU.

Table 8.7-6: Data to be collected 24, 36, 48 & 60 Month Cross-over Visits (COV6, COV7, COV8, COV9)

Data Collection	Location of Source
Average seated office BP Measurement per guidelines (including standing office BP)	Maintain at site
Medical History Review	Maintain at site
Limited physical examination including height, weight, brachial circumference; abdominal circumference; heart rate	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to BioClinica as requested
Protocol Deviations	Maintain at site

More frequent FU than those specified above are at the discretion of the Investigator and will be documented as unscheduled visits.

8.8. *Unscheduled Visits*

Unscheduled visits may occur at any time during the study for the assessment of, for example, possible adverse events and/or medication changes. Each unscheduled visit will be documented. In the event that an in-person visit is not allowed due to COVID-19, an unscheduled visit may be conducted remotely.
As part of the Unscheduled Follow-up, if any of the following assessments/procedures are performed, they should be recorded in the database: Medical History; Physical Examination; Medication Changes; Office Blood Pressure; Home Blood Pressure; Ambulatory Blood Pressure; 12-lead ECG; Non-invasive imaging (CTA/MRA) or other imaging; Urine Chemistry; Blood Chemistry; and Pregnancy Test.

8.9. *Study Completion*

All patients will be followed for a minimum of 60 months post procedure unless otherwise informed by the Sponsor. Documentation of study completion will be required for all subjects independent of the point at which they complete the study (including screening failure, early withdrawal or loss to FU, as applicable).

8.10. *Study Closure*

The point at which all subjects have completed the study will mark the point of study closure. The Sponsor will provide written documentation of study closure.

8.11. *Changes in Anti-Hypertensive Medication*

Throughout the study, subjects will be instructed about the importance of medication adherence. Compliance to the protocol will be assessed through the measurement of anti-hypertensives in urine at Baseline (post washout/run-in), 2, 6, and 12 months.

Subjects should be advised to contact their Investigational Center in the event that they have concerns which may lead them to restart anti-hypertensive medication. It is recommended that in these events, the subject is brought in for an unscheduled visit where their BP may be accurately evaluated. In the event that an in-person visit is not allowed due to COVID-19 public health emergency, an unscheduled visit may be conducted remotely.

For the period of washout/run-in prior to procedure, through to the 2-month Primary Efficacy endpoint visit, changes in medication outside the requirements of the study protocol may not occur other than:

- As required to facilitate anti-hypertensive drug washout per standard Institutional guidelines
- In the incidence of a BP Emergency associated with clinical events believed to be related to persistent or elevated hypertension
- In the incidence of a clinical event in which a change in medication becomes medically necessary.

Subjects will be asked to take any required study-defined anti-hypertensive treatment at approximately 08:00am daily except on the morning of each office FU visit when they will be asked to bring their protocol-defined medication with them to the visit.

8.11.1. Changes in Anti-Hypertensive Medication (Between 2- and 6-months FU)

Subjects are required to remain free of anti-hypertensive medication through to the 2-month Primary Efficacy endpoint visit unless necessitated as described above in Section 8.11. Following the 2-month Primary Efficacy endpoint visit, all subjects will remain blinded through the 12-month visit.

Introduction of antihypertensive therapy will occur as needed to achieve blood pressure control following the completion of the 2-month FU Visit (including ABP). If the average Home BP is <135/85 mmHg, no action is required.

Between the 2- and 6-month FU visits, a pre-defined protocol for escalation of anti-hypertensive medication is required for subjects whose BP is not controlled. At each FU visit between 2- and 6-months, blood pressure control must be evaluated. If control is not achieved at any follow-up visit during this period, anti-hypertensive medication must be started or escalated to the next step sequentially, in the order indicated in Table 8.11-1, unless otherwise medically indicated. If the escalation is not followed, the site will be requested to provide supporting justification.

- The medication escalation will start at the FU visit where a sustained elevation (≥135 mmHg systolic OR ≥85 mmHg diastolic) in average Home BP is recorded and confirmed by an average Office BP ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic. If elevated hypertension is sustained over 3 consecutive days, then medication escalation is recommended.
- If an in-office blood pressure cannot be obtained due to the COVID-19 public health emergency, the Home BP Diary will be used to confirm the need for clinical intervention.
- Drugs will be added sequentially at each monthly FU visit in the event BP remains uncontrolled. If medication escalation steps are not followed in order, justification must be provided.
- Medication escalation will be at the discretion of the Investigator if only average Home BP or only average Office BP meets the criteria above.

Table 8.11-1: RADIANCE II Drug Escalation

Escalation Step	Drug Class	Recommended drugs
0	None	NA
1	Long acting dihydropyridine CCB: mid dose	Amlodipine: 5 mg
2	ARB or ACEi: full dose	ARB: Valsartan 160-320 mg; Olmesartan 20-40 mg ACEi: Ramipril 10-20 mg; Lisinopril 20-40 mg
3	Thiazide diuretic: low dose	HCTZ 12.5 mg
4	Thiazide diuretic: full dose	HCTZ 25 mg
5	Long acting dihydropyridine CCB: full dose	Amlodipine 10 mg
Note: All recommended doses are once daily		

After completion of the 6-month visit, including the ABP recording, subjects are eligible to be treated per physician discretion.

8.11.2. Medication Changes due to BP Emergency (Safety Escape Criteria)

At all times, the safety and well-being of the subject are of primary concern.

Since the aim of RADIANCE II is to demonstrate the effectiveness of renal denervation without medication changes confounding the results, it is intended that subjects remain free of any anti-hypertensive medication through the Primary Efficacy endpoint visit which occurs 2-months post randomization. However, in cases where medication changes are considered medically necessary, anti-hypertensive medication and/or doses may be adjusted according to the following guidelines:

8.11.2.1. High BP Action

Clinical intervention may be required for patients who have clinical adverse events felt to be related to persistent or elevated hypertension, including hypertensive emergency[3], as defined by any of the following:

- Average Home BP ≥170 mmHg systolic or ≥105 mmHg diastolic, and subsequently confirmed by an average Office BP ≥180 mmHg systolic or ≥120 mmHg diastolic.
- Daytime ABP ≥ 170 mmHg systolic or ≥ 105 mmHg diastolic

If an in-office blood pressure cannot be obtained due to the COVID-19 public health emergency, the Home BP Diary will be used to confirm the need for clinical intervention.

During Screening (Prior to Randomization) - in the event of elevated BP as defined above, with associated clinical events felt to be related to persistent or elevated hypertension, the subject will be treated per Institutional guidelines and withdrawn from the study (Safety Escape Criteria).

If a subject meets the blood pressure criteria as described above, but is not experiencing related clinical events, withdrawal (pre randomization) or medication escalation (post randomization) is per physician discretion.

After Randomization, in the event that elevated BP as defined above (i.e. with associated clinical events felt to be related to persistent or elevated hypertension) is documented, the treatment regimen should follow the hypertension medication escalation algorithm as described in Table 8.11-1. All changes in antihypertensive treatment will be documented and patient BP data will be included as per intention-to-treat.

8.11.2.2. Low BP Action

Clinical intervention may be required for patients who have clinical adverse events felt to be related to persistent or reduced blood pressure as defined by any of the following:

- Office Systolic BP reduced to <110 mmHg with associated signs and symptoms of hypotension, or
- Reduced renal perfusion or an increase in creatinine ≥ 30%

[3] Hypertension Definitions used in the RADIANCE II Clinical Study are defined in the RADIANCE II DSMB Charter

If an in-office blood pressure cannot be obtained due to the COVID-19 public health emergency, the Home BP Diary will be used to confirm the need for clinical intervention.

The dosage of study-defined drugs can be reduced temporarily or discontinued permanently for subjects experiencing hypotension (as defined above) and/or hypotensive emergency requiring hospitalization[4]. The order in which anti-hypertensive drugs should be discontinued will depend upon the stage that the subjects are within the scheduled FU and the status of drug escalation (if any).

For all subjects in whom hypertension medication escalation has started since the 2-month FU visit, down-titration or discontinuation of anti-hypertensive medication should follow the reverse order in which they have been added such that the last drug added should be first stopped (followed by the penultimate drug, etc.).

All changes in antihypertensive treatment will be documented and patient BP data will be included as per intention-to-treat.

9. Study Defined Procedures/Testing

9.1. *Office and Home Blood Pressure Devices*

All clinical sites will be provided with validated, commercially available BP systems that will be used for the measurement of office and home BPs. Office BP should be recorded with the same device at every FU. Subjects will be trained on the use of Home BP devices.

9.2. *Ambulatory Blood Pressure Devices*

Ambulatory BP measurements at Baseline, 2, 6 and 12 month FUs and Cross-over Baseline, 2, 6 and 12 month FUs will be recorded with a validated ABP system provided by the ABP core lab. The same ABP device should be used for each FU for each individual subject. Subjects will be trained on the use of all BP devices. If an in-person study visit is not possible due to COVID-19 public health emergency, remote placement of the ABP system, under the guidance of site study staff, is permitted. Instruction using video conferencing or equivalent is strongly recommended. Remote placement of the ABPM will be documented in the EDC.

9.3. *Blood Pressure Measurements*

9.3.1. Measurement of Office BP

Measurement of average office BP is required for all clinic visits other than Discharge, where it is optional. Office BP measurements at all FUs post-discharge will be done by study personnel blinded to the subjects' randomization. All efforts will be made to ensure that measurement of office BP is standardized at each visit under similar conditions including measurement from the same arm at same time of day using the same device by the same person.

The measurement of office BP will be done according the following guidelines based on the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults. Specific Instructions on how to calculate average office BP will be provided by the Sponsor:

[4] Hypotension Definitions used in the RADIANCE II Clinical Study are defined in the RADIANCE II DSMB Charter

- Step 1: Properly Prepare the Patient
  1. Have the Patient Relax, sitting in a chair (feet on floor, back supported) for > 5min
  2. The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement
  3. Ensure the patient has emptied his/her bladder
  4. Neither the patient nor the observer should talk during the rest period or during the measurement
  5. Remove all clothing covering the location of cuff placement

- Step 2: Use Proper Technique for BP Measurements
  - Use a BP measurement device that has been validated
  - Support the patient's arm (e.g., resting on a desk)
  - Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum)
  - Use the correct cuff size, such that the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used

- Step 3: Take the Proper Measurements
  - At the first visit, record BP in both arms. Use the arm that gives the higher systolic reading for subsequent recordings.
  - Separate repeated measurements by 1-2 min

9.3.2. Measurement of Home BP

All subjects will be provided with a validated Home BP monitor with a cuff size appropriate to fit the arm. Verify that the BP recorded between the two arms is insignificant. If differences are significant (>10mmHg), instruct the subject to use the arm with the higher systolic readings. Subjects will be educated on the use of all the equipment necessary to record and report their home BP as well as the fact that individual BP readings may vary substantially. The subject should also be given instructions on how the Investigational Site would like to be contacted in the event that they have concerns related to the readings that are being recorded. Subjects will measure their BP at home during the 7 consecutive days prior to each scheduled office FU visit post-randomization up to and including the 12 month FU. The clinical site should contact the subject to remind them when to begin their 7 day Home BP monitoring and to bring their device and Diary with them to each FU. The Home BP monitors should be returned to the clinical center in the event that a subject withdraws or is screened out at any time prior to randomization. The following guidelines for measuring home BP should be followed:

- Take measurements in a quiet room
- Avoid smoking, caffeinated beverages or exercise within 30 mins before measuring BP
- Sit quietly for ≥ 5 min before BP measurements
- Sit with back straight and supported (on a straight-backed dining chair for example rather than a sofa) with feet flat on the floor and legs uncrossed. Keep arm supported on a flat surface (such as a table) with the upper arm at heart level.
- The bottom of the cuff should be placed directly above the bend of the elbow
- Take at least 2 BP measurements 1-2 minutes in the morning before taking medications and the evening before dinner.
- Ensure that the same arm is used for all Home BP measurements.

9.3.3. 24-hr ABP Measurements

- The ABP recording should be done consistently at each timepoint, either during the week (Monday-Friday) or on the weekend (Saturday-Sunday). Every effort should be made to collect ABP recordings during a consistent part of the week for each subject.
- In order to decrease variability in blood pressure collection, it is recommended that all ABPMs be started and stopped at around the same time of day for each subject. This includes any ABPMs that may need to be initiated remotely (see below).
- Subjects should be on stable anti-hypertensive medications (if applicable) for at least 2 weeks prior to the start of each ABP recording.
- The ABP system will be provided with an appropriate cuff size for the person's arm.
- The cuff will be attached to the patient's non-dominant arm after they have had their office BP recorded. System set up (including choice and fitting of BP cuff) subject instructions for use will be included in the BP Measurement Guidelines.
    - If an in-person study visit is not possible due to COVID-19 public health emergency, remote placement of the ABP system, under the guidance of site study staff, is permitted. Instruction using video conferencing or equivalent is strongly recommended. Remote placement of the ABPM will be documented in the EDC.
- Instruct the subject that the ABP recording must be for a minimum period of 24-hrs
- Instruct the subject that they may not remove the BP cuff during the 24-hr period of recording even when washing
- Instruct the subject that during the period in which measurements occur, that they should relax their arm and try not to walk or speak
- Instruct the subjects to return approximately 24-hrs later with the ABP Monitor to download the ABP data; if the device cannot be returned in-person, it may be sent via a certified overnight carrier.
- BP will be measured every 20 minutes during daytime (07:00-22:00 hours) and every 30 min overnight (22:00-07:00 hours). The first hour of recordings will be excluded as a "white coat window"
- Only ABP recordings with a minimum of 21 measurements during the daytime period AND 7 measurements during the nighttime period will be considered valid[xxxviii]. In case of a non-valid measurement, a known or suspected technical failure of the ABPM device, patient non-compliance to the study requirements (e.g. removal of cuff during recording, sleeping during the daytime period, etc.), a new ABP recording can be performed, preferably the next day. In the event of a repeat ABPM for reasons other than technical failure, the Sponsor must be notified for agreement. In the event that a response from the Sponsor cannot be obtained in a timely manner, do not delay the repeat ABPM. For analysis, the *first* valid ABP received will be used.

9.4. *Standardized eGFR Calculation*

eGFR calculations for both inclusion and FU measurements will be standardized using the Modification of Diet in Renal Disease formula (GFR (mL/min/1.73 m^2) = 175 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American) (conventional units). Formulas may be adapted to allow for non-US conventions. Data collected on the case report form will allow automatic calculation of eGFR.

9.5. *Non-Invasive Imaging (CTA/MRA)*

Evaluation of the kidneys to verify anatomical inclusion is required prior to the procedure using either standard Computed Tomographic Angiography (CTA) or Magnetic Resonance Angiography (MRA). Any good quality renal CTA or MRA imaging with arterial phase contrast that has been performed within 1 year of the subjects informed consent is considered eligible, however if not available, a CTA or MRA needs to be performed specifically for entry into the study. At a minimum, the site in collaboration with the Sponsor will perform and document an initial review of the image prior to the procedure. The Sponsor review is designed to allow recommendations for treatment strategy to be made prior to the procedure. A comparative renal CTA or MRA will be performed at 6-months after the procedure. An additional FU renal CTA or MRA will be performed at 12-months after the procedure only in subjects randomized to Treatment. Sham subjects that Cross-Over to Treatment will be required to have an additional CTA or MRA at 12-months post cross-over procedure. Additional imaging may be required at any time, if clinically indicated. To ensure consistency around image collection, guidelines for completion of CTA/MRA imaging will be provided by the Sponsor. If a follow-up CTA or MRA cannot be performed as per the visit window in Table 8.1-1 or Table 8.1-2, the imaging may be performed up to 90 days beyond the end of the visit window and still count towards that visit. This must be documented as a protocol deviation.

9.6. *Laboratory Assessments*

All subjects will have fasting blood collected at Baseline and 2, 6 and 12 month FU visits for full metabolic panel assessment (sodium, potassium, calcium, chloride, bicarbonate, glucose, uric acid, total protein, triglycerides, total cholesterol, HDL, HbA1C, blood urine nitrogen and serum creatinine). Documentation may be provided to support any local or national differences in standard metabolic panel collection. In addition, all subjects will have urine samples collected at Baseline and 2, 6, and 12 month FU visits for urinalysis (sodium, potassium, protein, albumin, creatinine). Females of childbearing potential will have a urine or blood plasma pregnancy test within 7 days prior to the procedure.

9.7. *HP LC-MS/MS of Antihypertensive Compliance*

HP LC-MS/MS is a recognized method with good to excellent sensitivity and specificity to detect many pharmacological agents in urine.[xxxix] Urine collected at Baseline, 2, 6 and 12 month FUs will be sent for analysis. Details of the analysis will be provided separately.

9.8. *Patient Preference Data*

Patient preference data is recognized as an important component of assessing the benefit – risk profile of an interventional based approach to treat hypertension. Patients have many options and are educated about their health and associated risks. It is extremely important to understand what is important to patients and how they assess benefit – risk of a procedure. Patient preference data was collected as part of RADIANCE-HTN via direct to patient outreach via social, and other, media, and on-line patient questionnaires. Patient preference data will also be collected during RADIANCE II either through approved social or other media, or more traditional quantitative and qualitative methods such questionnaire or interviews.

9.9. *Quality of Life (QoL) Data*

Subjects will be asked to complete Quality of Life (QoL) questionnaire(s), including at a minimum, the EQ-5D-5L. Patient Quality of Life data will be collected and compared.

The validated EQ-5D-5L is a generic questionnaire for describing and valuing health. It is based on a descriptive system that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Eligible patients will complete the questionnaire at Screening, Baseline, 2, 6- and 12-months FU.

10. Data Collection and Statistical Analysis

10.1. *Data Collection, Processing, and Review*

Subject data will be collected via a limited access, secure, electronic data capture (EDC) system meeting the requirements of 21 CFR part 11. Paper case report forms (CRFs) may be used as a back-up in the event that the EDC system becomes unavailable. Electronic and/or written signatures will be collected in compliance with local regulations.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system if used and will be issued to the clinical site for appropriate response.

In the event that any data has to be collected on paper CRFs, the clinical site will be required to re-enter the same data into the EDC system should it become subsequently available. The clinical site will record data on outcome variables as well as adverse events should they occur. Subject confidentiality will be maintained, and each subject will be identified by his or her subject number. Subject names will not be published.

For any data collected at clinical centers in France, data processing will be in accordance with the law (2004-806 of August 09th 2004) and will respect the directives of the national authority (CNIL: Commission National Informatique et Libertés, Law n° 78-17 of January the 6th 1978).

Each data field completed via an EDC system (or paper CRF) is expected to have a verifiable source document. Appropriate source documents include but are not limited to:

- Patient information sheet and consent form
- Subject Medical Record
- Screening logs
- Laboratory or core lab reports
- Cath Lab or Operating Room reports
- Angiograms; CTAs; MRAs
- Documentation of serious adverse events
- Worksheets* (for collection of data points that have no other verifiable primary source)

**Worksheets alone are usually not considered an acceptable primary source for key information related to inclusion/exclusion criteria or outcome data.*

10.2. *Statistical Analysis*

Any details of statistical analysis not included in the protocol, can be found in the Statistical Analysis Plan (SAP). The primary analysis will be based on the intent to treat population, with subjects analyzed according to their original randomization assignment. Per protocol and As Treated populations will also be defined.

10.3. *Primary Efficacy Endpoint*

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 with missing FU ABP values, a value of zero will be used in the analysis; this corresponds to imputing the baseline value. All details regarding the Primary Efficacy Endpoint will be provided in the SAP.

10.4. *Secondary Efficacy Endpoint*

The statistical analysis of the secondary efficacy endpoints will follow the methodology of the primary Efficacy Endpoint.

10.5. *Primary Safety Endpoint*

All adverse clinical events will be collected, coded and reported, for the duration of the study according to the definitions of ISO: 14155: 2011 (see Section 12.1).

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/m^2 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 composite MAE for the treatment arm will be compared to a 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.

10.6. *Observational Assessments*

For continuous measures, the linear model methodology of the Primary Efficacy endpoint will be applied. For categorical variables, binomial proportions and their corresponding exact 95% confidence intervals will be calculated. Differences between proportions will be assessed via Fisher's exact test. Nominal p-values will be used without adjustment for multiple comparisons. Additional exploratory analyses may be performed including analysis of durability of effectiveness.

10.7. *Control of Systematic Error/Bias*

Minimizing potential sources of bias has been taken into consideration in study design. To minimize selection bias, subjects will be randomly assigned to treatment or control only after completion of all screening and eligibility procedures. Randomization will be generated by computer and stratified by center using blocks of small size and treatment permutation.

10.8. *Limits on Subjects Enrollment*

Randomization at any single clinical center will be limited to 20% of the maximum randomization in order to prevent a single center from unduly influencing the study results. In addition, a maximum of 50% of subjects may be randomized in clinical centers outside the United States. Clinical centers will be informed in writing by the Sponsor when they have met any of the enrollment limits.

10.9. *Planned Interim Analyses*

No formal interim analyses are planned for the purpose of stopping this study early, for declaring effectiveness or for futility. Any interim analyses planned for the purposes of adjusting sample size will be documented in the SAP. Interim datasets will be provided to the DSMB for the purposes of review of safety.

10.10. *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. Details of these analyses will be described in the SAP. Additional exploratory subgroup analyses may be performed.

10.11. *Multivariable Analyses*

The primary analysis of the Primary Efficacy endpoint will be based on a linear model with terms for randomized treatment group and baseline BP. Additional exploratory analyses may be performed as described in the SAP.

10.12. *Core Laboratories*

Core laboratories and/or independent experts will be used to assess and centralize non-invasive imaging, ABP data and clinical events. Specific details related to the core laboratories will be provided in separate Manuals of Operations.

10.12.1. Imaging Core Lab/ Independent Radiologists

An imaging core laboratory, run by the Cardiovascular Research Foundation (CRF), will review all follow-up CTA/MRA including the 6 month FU visit required imaging for all subjects and the 12 month FU imaging required for subjects randomized to treatment. The CRF core lab will access the imaging studies through the BioClinica image database called BioClinica SmartSubmit which will be used to store all images associated with the RADIANCE-II Study. Each site will be provided access to the BioClinica Image database for upload capabilities. The core lab will compare to baseline pre-procedure CTA/MRA and procedural angiographic imaging. Additionally, the core lab will review all follow-up CTA/MRA obtained for any reason during the course of the study.

Details of the imaging core lab responsible for reviewing CTA/MRA imaging are provided below:

Clinical Trials Center Services
Cardiovascular Research Foundation
1700 Broadway 9th Floor
New York, NY 10019
USA

The imaging core laboratory will not be used to determine anatomical eligibility. Eligibility will be determined by the site however Independent radiologists, contracted by the Sponsor, may assist in the review of pre-procedure imaging to assess for pre-existing pathology, and anatomical exclusions that would deem the subject ineligible per the protocol. Subjects with evidence of any renal artery anatomy anomalies that are outside the protocol inclusion/exclusion criteria will be documented as ineligible for randomization in any per protocol analysis.

10.12.2. Ambulatory Blood Pressure Core Lab (dabl Ltd)

Details of the core lab that will be used for configuration, distribution, training and centralization of data collection for 24-hr ABP measurements taken at Baseline, 2, 6 and 12- month FUs are provided below:

dabl Ltd,
Carraig Court,
Georges Avenue,
Blackrock,
Co. Dublin,
Ireland
T: +353 (0) 1 278 0247
F: +353 (0) 1 278 0882
www.dabl.eu

10.12.3. Anti-Hypertensive Drug Adherence Core Lab

Details of the core lab responsible for the determination of adherence to anti-hypertensive medications, are provided below:

Department of Chemical Pathology & Metabolic Diseases
University Hospitals of Leicester Pathology Services
Leicester Royal Infirmary,
Infirmary Square,
Leicester, LE1 5WW,
United Kingdom

11. Safety Reporting

11.1. *Definitions and Classification*

Adverse Events (AEs) are classified as per ISO:14155:2011 as "any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device". All AEs will be collected for the duration of the study and will be further classified as anticipated or unanticipated using the known risks associated with the study device documented in Section 12. AE classification will be according to the following definitions as provided in Table 11.1-1.

Table 11.1-1: Adverse Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device

Table 11.1-1: Adverse Event Definitions

Term	Definition
Ref: ISO 14155-2011	NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. NOTE 3: This definition includes any event that occurs during the renal denervation procedure including the renal angiogram
Serious Adverse Event (SAE) *Ref: ISO 14155-2011*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011*	Adverse device, or procedure related, effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Underlying diseases/ pre-existing conditions will not be reported as an AE unless there has been a substantial increase in the severity or frequency of the problem which has not been attributed to natural history during the course of the investigation.

In general, death should not be documented as an AE, but rather be reflected as an outcome of a specific SAE (see Table 11.1-1 for AE definitions).

Any AE experienced by the study subject after informed consent, whether during or subsequent to the procedure, must be recorded (EDC and/or paper CRF).

11.2. *Relationship to Study Device(s) or Procedure*

The Investigator will assess the relationship of any AE to the study device and study procedure per ISO 14155:2011 / MEDDEV 2.7/3. During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Protocol or the risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

In the event of any discrepancy with respect to the relationship (e.g. during internal, independent adjudication, or DSMB review), the site may be queried for clarification. SAEs deemed to be specifically related to use of the study device (e.g. renal artery dissection or perforation, new onset renal stenosis) will be reported separately from SAEs related to the procedure but not specific to renal denervation (e.g. anesthesia-induced nausea; allergy to contrast, etc.).

The sponsor and the investigators will use the definitions shown in Table 11.2-1: to assess the relationship of the adverse event to the investigational medical device or procedures.

Table 11.2-1: Definitions for Assessing Relationship of AE to Study Device or Study Procedures (*ref ISO 14155:2011/MEDDEV 2.7/3*)

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; - harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

11.3. *COVID-19 Related Adverse Events*

Adverse events will be evaluated to determine relatedness to COVID-19. The PI will assess the relationship of the AE to COVID-19 in the Adverse Event eCRF. AE classification will be according to the following definitions as provided in Table 11.3-1.

Table 11.3-1 COVID-19 Adverse Event Definitions

Term	Definition
Related	Subject tested positive for COVID-19 and the event occurred < 60 days after testing.
Possibly related	Subject experienced or treated for signs/symptoms including any respiratory infections related to COVID-19 without a positive test and the event occurred < 60 days from the above-mentioned signs/symptoms.
Not related	Subject tested negative COVID-19 test (Or) subject tested positive for COVID-19 or experienced signs/symptoms including any respiratory infections related to COVID-19 but not contributing to the event or the event occurred > 60 days from the above-mentioned positive test or signs/symptoms. (Or) subject was not tested for COVID-19 and did not experience any related/symptoms including any respiratory infections.

11.4. *ReCor Medical Device Deficiencies*

Device deficiencies related to the use of ReCor Medical products may occur in the absence of any associated AE but must still be reported. The definition of a potential device deficiency is provided in Table 11.4-1.

Table 11.4-1: Device Deficiency Definition

Term	Definition
Device Deficiency *Ref: ISO 14155:2011*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to the Sponsor within 2 business days of notification. If possible, the device(s) and all associated accessories will be returned to the sponsor for analysis. Instructions for returning the clinical device(s) will be provided. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record. Failure to access the renal artery may be reported as a device deficiency.

In the event that a device deficiency is associated with an AE that specific event would be recorded as an AE.

Note: any Device Deficiency that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered reportable and should be notified to ReCor Medical within the timeframe noted.

11.5. *Investigator Reporting Responsibilities*

The timelines for reporting AEs and device deficiencies to ReCor Medical are shown in Table 11.5-1.

Table 11.5-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE CRF page with all available new and updated information. In the absence of access to the EDC system, an email to ReCor medical with all available information is recommended	• Within 1 business day of first learning of the event
Serious Adverse Event including Serious Adverse Device Effects	Complete AE CRF page with all available new and updated information.	• Within 2 business days or sooner (if required by local/regional regulations) of first learning of the event
Device Deficiencies	Complete Device Deficiency CRF page with all available new and updated information.	• Within 2 business days of first learning of the event or as per local/regional regulations
Adverse Device Event	Complete AE CRF, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Within 10 business days or sooner (if required by local/regional regulations) of first learning of the event
Adverse Event	Complete AE CRF, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Within 30 business days or sooner

11.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

11.6.1. Sponsor Responsibilities

The Sponsor is responsible for reporting all clinical events (including UADEs, SADEs and SAEs) reported by Investigators to applicable regulatory agencies as required by 21 CFR 812.150(b), ISO 14155:2011/MEDDEV 2.7/3, and any other applicable geographies' requirements. In addition, the Sponsor is responsible for periodic progress reports to all reviewing IRBs/ECs, participating investigators and regulatory authorities, as appropriate and required per local/national regulations.

11.6.2. Investigator Responsibilities

The Principal Investigator is responsible for informing the Sponsor and the reviewing IRB/EC of all UADE's, SADEs and SAE's in line with the protocol and as required by local/national regulations.

12. Potential Risks and Benefits

12.1. *Risks Associated with the Study Device(s)*

There are potential (anticipated) risks associated with the use of the Paradise system. These risks may be serious or non-serious and include but are not limited to:

- Ablation or thermal injury to vessel, adjacent tissue or other structures from energy application
- Abdominal pain
- Acute kidney injury
- Adverse drug reaction
- Allergic reaction (drug, contrast, device or other)
- Angina pectoris
- Anxiety
- Arrhythmia
- Atrial tachycardia
- Arteriovenous fistula
- Arterioenteric fistula
- Bleeding
- Bradycardia
- Cardiopulmonary arrest
- Complications related to pain and anti-anxiety medication protocol
- Death
- Deep vein thrombosis
- Diarrhea
- Dizziness/Syncope/Weakness
- Edema
- Embolism (air, plaque, thrombus, device or other)
- Headache
- Hematoma
- Hematuria
- Hemorrhage
- Hyperhidrosis
- Hypertension, including hypertensive crisis
- Hypotension, including Orthostatic hypotension
- Infection
- Myocardial infarction (MI)
- Nausea
- Pain (back, access site)
- Pulmonary embolism
- Pseudoaneurysm
- Renal artery aneurysm or pseudoaneurysm
- Renal artery dissection, or perforation
- Renal artery stenosis or acceleration of atherosclerotic disease
- Renal failure or renal insufficiency
- Renal infarction (including due to embolization of plaque or coagulated/charred blood or tissue)

- Sepsis
- Stroke
- Transient ischemic attack and/or Cerebrovascular accident
- Urinary tract infection
- Vasospasm
- Ventricular tachycardia
- Vessel trauma (perforation, dissection, or rupture)
- Vessel thrombosis or occlusion
- Vomiting

12.2. *Risks associated with Percutaneous Arterial Catheterization*

There are known (anticipated) risks associated with the arterial catheterization procedure not specific to the renal denervation system. These risks may be serious or non-serious and include but are not limited to:

- General complications
    - Cardiorespiratory arrest
    - Severe arrhythmias or cardiac conduction defects
    - Acute coronary syndrome
    - Acute heart failure
    - Hypertensive crisis
    - Stroke from any cause
    - Pulmonary embolism
    - Acute renal insufficiency, hemodialysis
    - Doubling of serum creatinine
    - Retro-peritoneal hemorrhage/hematoma
    - Allergic reaction to contrast agent
    - Infection
    - Hypotension
    - Mild disturbances of heart rate or cardiac conduction
    - Proteinuria, hematuria, electrolyte disturbances
    - Fever
    - Pain
    - Access site hematoma
- Arterial complications associated with catheterization of the renal arteries
    - Embolism, infection
    - Stenosis or aneurysm
    - Dissection/perforation
    - Arterio-venous fistula or pseudoaneurysm
    - Need for revascularization by bypass surgery or angioplasty, stenting or surgery
    - Arterial spasm (vasospasm)
- Arterial complications associated with catheterization of the Aortic or illio-femoral arteries
    - Embolism and/or thrombosis
    - Dissection/perforation
    - Peripheral ischemia
    - Cholesterol embolism
    - Need for revascularization by bypass surgery or angioplasty, stenting or surgery

- Femoral/Vascular access site complications
    - Arterial dissection/rupture
    - Access site hematoma/hemorrhage
    - Arterio-venous fistula
    - Pseudoaneurysm
    - Need for arterial bypass surgery
    - Infection
    - Pain
    - Bruising
    - Swelling

12.3. *Risks Associated with Participation in the Clinical Study*

There may be additional risks associated specifically with participation in the RADIANCE II clinical study. These risks are primarily associated with the additional testing associated with the study design and include but are not limited to:

- Complications related to anesthesia/monitored anesthesia/conscious sedation
- Risks associated with blood draw
- Risks associated with non-invasive imaging and risk of radiation exposure including potential teratogenic damage, if pregnant
- Risks associated with the discontinuation of antihypertensive drug therapy
- Risks associated with the use of any Blood Pressure Monitoring system such as bruising, pain or skin rash related to the cuff
- Risks associated with a 12-lead ECG including a skin rash

12.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through appropriate training, compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or FUs and by promptly supplying ReCor Medical with all pertinent information required by this protocol. In addition, specific measures have been taken to minimize the risk for all subjects including:

- Drug discontinuation will occur in line with accepted Institutional guidelines for a subjects' current antihypertensive medication
- Clinical intervention may be required for patients who have clinical adverse events felt to be related to persistent or elevated hypertension as defined by any of the following:
    - Average Home BP ≥ 170 mmHg systolic or ≥ 105 mmHg diastolic and subsequently confirmed by an average office BP ≥ 180 mmHg systolic or ≥ 120 mmHg diastolic. If an in-office blood pressure cannot be obtained due to the COVID-19 public health emergency, the Home BP Diary will be used to confirm the need for clinical intervention. If elevated hypertension is sustained over 3 consecutive dates, then medication escalation is recommended.
    - Daytime ABP ≥ 170 mmHg systolic or ≥ 105 mmHg diastolic
- Drug discontinuation is limited to a short period of approximately 3 months during which timeframe subjects are a low risk of any CV event off treatment[xxxix]

- Subjects will be provided with a Home BP device and will be instructed to record their average home BP on the 7 consecutive days immediately prior to Baseline, 1, 2, 3, 4, 5, 6 & 12 month FUs
- Subjects will be seen every 4 weeks throughout the first 6 months of the study and antihypertensive drug therapy may be initiated at any follow-up in the event that high or low BP action is determined to be required (see Section 8.11)
- Subjects will have antihypertensive drug therapy initiated immediately following the 2 month FU if needed (see Section 8.11.1: Antihypertensive Drug Escalation)
- Non-invasive imaging (CTA or MRA) will be required for all randomized subjects at baseline and 6 month FU. An additional FU renal CTA or MRA will be performed at 12-months after the procedure only in subjects randomized to Treatment. Sham subjects that Cross-Over to Treatment will be required to have an additional CTA or MRA at 12-months post cross-over procedure. Additional imaging may be required at any time, if clinically indicated.

12.5. *Anticipated Benefits*

The RADIANCE-HTN SOLO Cohort provided initial data to support that ultrasound renal denervation with the Paradise System reduces blood pressure significantly more than sham in hypertensive subjects free from antihypertensive medication and with a good safety profile. Subjects included in RADIANCE II may benefit from closer evaluation of their hypertension via frequent office FU, home and 24-hr ABP measurements. They may also benefit from having diagnostic non-invasive and invasive evaluation of their renal anatomy in the event of previously undiagnosed renal abnormalities or stenosis. There is potential that subjects may have their hypertension reduced without the need for medication. There may be no benefit to subjects.

12.6. *Risk to Benefit Rationale*

Catheter based renal denervation is an interventional approach to treat patients with essential hypertension by interrupting the renal sympathetic nerve signaling pathways. Chronic elevation in sympathetic activity contributes to the development of chronic hypertension, and potential end organ damage. Chronic essential (primary) hypertension is a major public health burden with a global prevalence of 1 billion, and a US prevalence of approximately 76 million. Hypertension is considered to be a major risk factor for cardiovascular diseases, specifically stroke, myocardial infarction, heart failure, and renal failure, and accounts for approximately 9 million deaths worldwide annually. Despite the associated morbidity and mortality, BP control remains a challenge globally in part due to issues of non-compliance to prescribed medications. The premise is that ablation of renal sympathetic nerves will lead to a decrease in BP either as an adjunct to pharmacologic therapy, or potentially as a replacement of escalating pharmacologic therapy. Incremental reductions in BP are known to decrease the incidence of major cardiovascular events. Reducing systolic BP by as little as 5 mmHg has been shown to be associated with a 14% reduction in the incidence of stroke, a 9% reduction in the incidence of cardiovascular disease and a 7% reduction in mortality.

The use of ultrasound energy to ablate the nerves may provide for a safe and effective approach to decrease blood pressure through renal nerve denervation. The Paradise System has been designed to maximize safety while ablating the nerves in a circumferential pattern to effectively ablate the majority of the renal sympathetic nerves. Ultrasound energy offers distinct advantages over other energy sources since direct tissue contact is not required, and

the energy profile is controllable. The Paradise System has been designed to deliver energy for a short duration, at a target mean depth of 1-6 mm to ablate the renal sympathetic nerves located in the adventitia and peri-adventia while preserving the integrity of the renal arterial wall (0-1 mm) and by preventing thermal injury to non-target tissues at depth (maximum depth >10mm). Preclinical studies confirm the target ablation profile is consistently achieved with effective nerve ablation and minimal to no injury to non-target tissues.

The clinical procedure is a standard interventional cardiology procedure that can be performed quickly with minimal injury to non-target tissues. Ablation of nerves can be painful however the procedure is tolerable with appropriate analgesic medication. The Paradise System has been evaluated in multiple clinical studies with few AEs reported specifically related to the use of the investigational system. Office and ambulatory BP has been reduced in a majority of patients. The benefit to patients in terms of reduction of cardiovascular events will need to be determined over a long duration however there is notable short-term benefit associated with the procedure in a majority of patients. Many patients experience large decreases in ABP, and in certain cases a concomitant decrease in antihypertensive medication. The procedure risks are limited to short-term pain, and standard angioplasty catheter related risks. Ultrasound provides for a safe means to ablate renal sympathetic nerves that should provide a benefit to patients with chronic essential hypertension in terms of BP reduction.

13. Protocol Deviations

The study protocol is to be followed at all times by Investigators and all personnel involved in the clinical study. The exception is in the event of an emergency deviation initiated by the Investigator in the case where a change is needed to eliminate the apparent hazard to subjects. Emergency deviations must be reported to ReCor Medical no later than 24 hours following the emergency.

All deviations from the protocol, including those occurring as a result of the COVID-19 public health emergency, will be documented (via EDC system and/or on CRF) and will be classified according to the categories below in Table 13-1:

Table 13-1: Deviation Classifications

Deviation Classification	Definition of Deviation	Timeline for Reporting (if applicable)
Class Ia	Deviation to protect the life or physical wellbeing of a patient in an unforeseen emergency	Within 24 hrs
Class Ib	Documented failure to obtain subject informed consent	Within 24 hrs of notice
Class II	Deviation based on medical judgment to prevent harm to a patient in a non-emergency situation	As soon as possible
Class III	Deviation due to lack of understanding of the protocol requirements (training is an issue)	As soon as possible
Class IV	Deviation due to a situation that is beyond control	As soon as possible
Class V	Deviation due to an oversight, error (training is not an issue)	As soon as possible
Class VI	Event that does not meet the strict criteria of Class I-V yet does not meet the criteria of the protocol. Includes situations wherein the sponsor allows a waiver.	NA

One protocol deviation per visit shall be entered to capture any/all deviations related to assessments not conducted per protocol due to COVID-19. Protocol deviations will be evaluated to determine relatedness to COVID-19 by the site. In the protocol deviation reporting, indicate whether visits and/or assessments were conducted remotely (e.g. by phone or video teleconference), late, or if visits were missed.

Deviations from the investigational plan and study requirements (including cGCP guidelines) will be reviewed and evaluated on an ongoing basis and appropriate corrective actions will be implemented as necessary.

14. Protocol Amendments

Changes to the study must be documented via a formal amendment process *prior to* implementation in the study. Amendments to the investigational plan may be initiated by ReCor Medical Inc. or at the request of the Investigator. A formal amendment cannot be initiated by an Investigator or clinical site personnel without the approval of ReCor Medical Inc. and the appropriate Local and National approvals including the documented approval of the Investigator.

15. Device/Equipment Accountability

Per FDA 21 CFR Part 812, Subpart G and ISO 14155-2011, the investigational devices/equipment shall be controlled and used only in this clinical study and according to this clinical protocol. Tracking of subjects and device allocations will be performed during the study.

The sponsor shall keep records to document the physical location of all study-related devices from shipment to the investigation sites until return or disposal. It is recommended that the Paradise catheter and accessories used for each procedure be returned to the Sponsor. If the devices are not returned, appropriate disposal must be documented. All unused investigational product will be returned to the Sponsor at the end of the study.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following:

- Date of receipt
- Identification of each investigational device/piece of equipment (model number/product description), serial/lot number)
- Expiry date (if applicable)
- Initials of person recording device receipt/return
- Date of use (if applicable)
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject /malfunctioned (if applicable)
- Reason for return

16. Compliance

16.1. *Statement of Compliance*

This study will be conducted in accordance with the declaration of Helsinki, ISO 14155: 2011 and FDA 21 CFR parts 50, 54, 56, 812. The study shall not begin until appropriate National and Local approvals have been obtained, as appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed where appropriate.

16.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with all Clinical Study Agreements, the clinical protocol, ISO 14155:2011, ICH/GCP, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject. In addition the Investigators are responsible for:

- Ensuring that the study is conducted with the express approval of the Institution's IRB/EC
- Ensuring that conducting the study will not give rise to conflicts of interest
- Informing the Sponsor in writing of the reason(s) for any withdrawal of any IRB/EC approval
- Ceasing the enrollment of subjects immediately in the event of the withdrawal of any IRB/EC approval
- Ensuring that no subjects will be enrolled, without prior, written Approval to Enroll from the Sponsor
- Agreeing to use their best efforts to satisfactorily complete the planned work and to comply at all times with accepted Good Clinical Practice
- Informing the sponsor of any conditions under which prior research was terminated
- Ensuring that informed consent is obtained appropriately and that the conditions of informed consent are complied with
- Ensuring the appropriate completion of all CRFs (paper and/or EDC) with the understanding that certain records and reports may be submitted to regulatory agencies by the Sponsor to support regulatory submissions
- Maintaining all records as described in the Protocol
- Supporting a monitor/auditor (as applicable) in their activities
- Informing the Sponsor of all adverse events and adverse device effects in a timely manner and informing the EC/IRB of any serious adverse device effects as applicable

16.3. *Institutional Review Board/ Ethics Committee*

The study shall not begin until appropriate National and Local approvals have been obtained, as appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed where appropriate.

A copy of the written IRB/EC and/or competent authority approval of the clinical protocol (or permission to conduct the study or appropriate equivalent) as well as IRB/EC approval of the Informed Consent Form, must be received by the Sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject. The Sponsor will provide a written "Approval to Enroll" to document the point at which all requirements for initial subject recruitment have been met.

Annual IRB/EC renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements.

16.4. *Sponsor Responsibilities*

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. Only authorized Sponsor personnel or a designated Sponsor representative will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by the Sponsor for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name. Authorized representatives of the Sponsor may be present at procedures and FUs to provide technical and study specific assistance and may assist with the collection of technical data via the use of Technical Source Forms (worksheets). Any data collected by the Sponsor representative will be verified and counter signed by the Investigator. The Sponsor representative will not:

- Practice medicine
- Provide medical diagnosis or treatment to subjects

In accordance with the requirements of providing technical support during the procedure and FUs, the Sponsors representative will not be blinded to randomization but will ensure that no information that in any way may un-blind the Sponsor, subjects or blinded clinical site staff, will be included in any reports (written or verbal).

16.5. *Insurance*

Where required by local/country regulation, the proof and type of insurance coverage, taken by the sponsor for subjects in the study will be obtained.

17. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. Monitoring will occur in line with the Study Monitoring Plan.

17.1. *Study Monitor*

Study Monitors assigned to the RADIANCE II study will fulfill the required Sponsor and monitor responsibilities. Monitors in collaboration with other Sponsor-designated personnel, will be responsible for reviewing the device accountability documentation and subject data as collected on CRFs or via an EDC system. The monitor will ensure that the clinical protocol has been approved by the IRB/EC and will assure ongoing compliance with clinical protocol.

The Investigator/institution guarantees direct access to original source documents by Sponsor personnel, their designees, and appropriate regulatory authorities.

In accordance with the requirements of role, study monitors will not be blinded but will ensure that no information that in any way may un-blind the Sponsor or blinded clinical site staff will be included in any reports (written or verbal).

17.1.1. Monitoring Procedures

Monitoring visits to the clinical sites will be made periodically for the purpose of ensuring that Investigators and their staff understand and accept their defined responsibilities, assessing compliance with current GCP guidelines, evaluating clinical trial progress, assessing the continued acceptability of the clinical site facilities, assessing compliance with this investigational plan, and verifying the data recorded on CRFs or via an EDC system. Remote monitoring of sites is permitted as allowable by the sites, local regulatory authority and/or the IRB/EC.

The Sponsor will design the forms to be used for the collection and recording of data at the clinical site. Investigators will be responsible for the timely completion and submission of these forms.

- Investigators are to maintain all source documents as required by the clinical protocol including but not limited to laboratory results, CRFs, supporting medical records, informed consents and applicable electronic files. The source documents will be used at the regular monitoring visits to verify information submitted on the CRFs. Clinical monitoring will include review and resolution of missing or inconsistent results to assure the accuracy of the reported data. Where any discrepancies are noted, they will be resolved with the Investigator and/or an individual designated by the Investigator. Where the data is incomplete, attempts will be made to obtain the missing data. The source documents and any completed CRFs will remain at the clinical sites.

Subject safety will be ensured by noting that the consent was properly documented, the investigational plan was followed, and that AEs were reported and followed-up as appropriate.

The study Monitor will evaluate and summarize the results of each clinical site visit in written reports, identifying any repeated data problems with any Investigator and specifying recommendations for resolution of noted deficiencies.

As required by the IDE regulations, the conduct and monitoring of the clinical investigation will be conducted in accordance with the Sponsor's approved monitoring plan.

18. Informed Consent

All subject participation is voluntary and as such Informed consent shall be obtained in writing from all subjects or their legally authorized representative. The process of obtaining informed consent shall be documented before any procedure specific to the clinical investigation is applied to the subject. The informed consent form consists of an information form and an informed consent signature form which can either be combined into one document or separated into two documents. The Sponsor will provide a template informed consent form in local language at a level understandable to the subject which will be

approved by the IRB/EC. Changes to the template are acceptable but will be reviewed and approved by the Sponsor. In the event that new information becomes available during the course of the study that may significantly affect a subjects' decision to continue participation in the study, it will be provided to all affected subjects in written form and may require that the subject re-sign and date an amended informed consent form or new informed consent form as applicable. Any changes to the informed consent form that occur during the course of the study will require approval by the IRB/EC.

18.1. *Process of Obtaining Informed Consent*

The process of obtaining informed consent must be followed per FDA 21 CFR Part 50.20 and/or ISO: 14155: 2011. The process of obtaining informed consent at a minimum shall include the following steps:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
- Not waive or appear to waive the subject's legal rights
- Use native non-technical language that is understandable to the subject
- Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
- Include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process
- Provide the subject with a copy of the signed and dated informed consent form and any other written information
- Show how informed consent will be obtained and recorded in special circumstances where the subject is unable to provide it him- or herself
- Ensure important new information is provided to new and existing subjects throughout the clinical investigation

The above requirements shall also apply with respect to informed consent obtained from a subject's legally authorized representative. Informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation. In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

The original informed consent form will be maintained at the clinical site. The subject will be provided with a signed and dated copy including any other written information.

Failure to obtain subject consent is a deviation to the study protocol and will be reported by the Sponsor to the appropriate Local and National authorities in line with their reporting requirements.

19. Committees/Boards

19.1. *Adverse Event Review*

AEs will be collected and reviewed on a continuous basis. Adjudication of AEs will occur in 4* stages:

- Stage 1: Investigator review and initial assessment of AE relationship to study device or study procedure.
- Stage 2: Sponsor review. Sponsor may query Investigator assessment in the event there are discrepancies with source.
- Stage 3: All events deemed to be potentially endpoint related will be reviewed by an independent Clinical Events Committee (CEC).
- Stage 4: The DSMB may provide final, independent review of aggregate events.

**Independent adjudication using persons qualified in the appropriate field may be used at any stage as required for appropriate review.*

19.2. *Clinical Events Committee*

The RADIANCE Clinical Events Committee (CEC) will be comprised of independent physician experts, and may include experts in hypertension, interventional radiology or cardiology, and diagnostic radiology. The CEC will be responsible for the review and adjudication of individual events which comprise the components of the primary safety endpoint, and the additional safety events outlined in Section 4.2.1. Adjudication of events will be based on a pre-defined definition of specific safety events. The CEC will adjudicate specific safety events for COVID relatedness, as described in the CEC Charter. The CEC will have access to all relevant source documentation, including core lab assessments of renal artery imaging. The CEC will meet on a regular basis to review events. Additionally, individual members of the CEC may review specific events, as needed, to ensure timely adjudication of events in the interval between committee meetings. Responsibilities, qualifications, membership, committee procedures, and definition of specific events to be adjudicated will be outlined in the CEC Charter.

19.3. *Data Safety Monitoring Board*

The RADIANCE Data Safety Monitoring Board (DSMB) is comprised of independent experts in hypertension, interventional radiology or cardiology and biostatistics. The DSMB is in place to ensure patient safety by evaluating all accumulating data and to provide recommendations to ReCor Medical, and/or the Principal Investigators regarding continuing, modifying, or terminating the study.

During the course of the study, the DSMB will review accumulating safety data in order to monitor the incidence of protocol-defined events and other trends that would warrant modification or termination of the study. The DSMB will review accumulating safety data for COVID relatedness, and the overall impact of COVID 19 to the study. The DSMB may review accumulating effectiveness data to assess the overall benefit-risk of the study. Criteria under which efficacy data may be un-blinded will be pre-defined and documented in the Statistical Analysis Plan, as will triggers related to specific AE rates that would warrant the stopping or termination of the trial. Responsibilities, qualifications, membership, and committee procedures will be outlined in the DSMB Charter.

19.4. *Steering Committee*

The RADIANCE Steering Committee is comprised of senior clinical, medical and regulatory members of ReCor Medical Inc. as well as International physician investigator advisors and the study statistician as appropriate. The role of the Steering Committee is to overview the design, submission and conduct of the study. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission however, ReCor Medical Inc. remains responsible for all decisions related to any such requests in line with approved study agreements.

20. Suspension or Termination

20.1. *Premature Termination of the Study*

ReCor Medical Inc. reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of UADEs that present a significant or unreasonable risk to subjects enrolled in the study
- An enrollment rate far below expectation that prejudices the conclusion of the study
- A decision on the part of ReCor Medical Inc. to suspend or discontinue development of the device

20.2. *Termination of Participation by Investigator/Withdrawal of IRB/ EC Approval*

Any investigator, or IRB/ EC involved in the RADIANCE II study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to ReCor Medical Inc. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.2.1. Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by ReCor Medical Inc. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by ReCor Medical Inc.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator when possible or another authorized clinical Investigator. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by ReCor Medical Inc.

The investigator must return all documents and investigational product to ReCor Medical Inc., unless this action would jeopardize the rights, safety, or welfare of the subjects.

20.3. *Criteria for Suspending/Terminating a Study Center*

ReCor Medical Inc. reserves the right to stop the inclusion of subjects at a study center at any time if no subjects have been enrolled for a period beyond 3 months after the site has been granted Approval to Enroll, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study-related devices and equipment, as applicable, will be returned to ReCor Medical Inc. unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the center will continue to be followed per protocol-defined FU. The Principal Investigator at the center must make provision for these FU visits unless ReCor Medical Inc. notifies the investigational center otherwise.

21. Reporting and Publication Policy

ReCor Medical Inc. is committed to the publication and dissemination of clinical study results. Any publication or presentation relating to the RADIANCE II will require that ReCor Medical's role as a sponsor or financial supporter is included. The final report of the conclusions of the study will be written within 12 months of the closing of the database at the end of the study. The report will be signed by all study principal investigators and provided to all study investigators. The study protocol will be registered at www.clinicaltrials.gov before the inclusion of any study subjects.

22. Reimbursement and Compensation for Subjects

Travel and other expenses incurred by subjects as a result of participation in the study may be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

23. Medicare Study Criteria (US Only)

Access to clinical study data provides opportunities to conduct further research that may help advance medical science and improve patient care. This helps ensure the data provided by research participants are used in the creation of knowledge and understanding. To this end, as stated in Section 22. Reporting and Publication Policy, the study results on all pre-specified outcomes, including negative outcomes, will be submitted to ClinicalTrials.gov not later than one year after the study completion date, where the completion date is defined as the date that the final subject was examined or received an intervention for purposes of data collection for the pre-defined outcome measures. Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early.

Subjects participating in the RADIANCE II study are eligible for antihypertensive drug therapy and following the general indications/contraindications for use of the Paradise Renal Denervation System, will be identified from the general subject population. Therefore, it is not anticipated the device under investigation will affect Medicare beneficiaries differently than it would the Medicare eligible patients found in the investigators general subject

population. However, participation in the study may provide Medicare beneficiaries with early access to a novel, investigational ultrasound renal denervation device therapy that is not otherwise available commercially in the U.S. at this time. According to 2012 CMS report on chronic conditions xl, high blood pressure (Hypertension) affects 58% of the Medicare FFS population including 39.5% of beneficiaries under 65 years old and 59.1% of beneficiaries age 65 and older. Recent analyses of National Health and Nutrition Examination Survey (NHANES) data, have estimated the prevalence of resistant hypertension at 8.9±0.6% of the US hypertensive population in 2003-2008. A time-sequence comparison of NHANES data from 1998 through 2008 suggests that, unlike hypertension, resistant hypertension is becoming more prevalent (e.g., 20.7% in 2005-2008), due to aging and increased obesity in the general population[xli]. Because the prevalence of hypertension is known to increase with age along with the potential for resistant hypertension, the results of this study are expected to be generalizable to the Medicare eligible population primarily due to age (e.g., the 65 years and older population).

24. Abbreviations and Definitions

24.1. *Abbreviations*

Abbreviations are shown in Table 24-1.

Table 24-1: Abbreviations

Abbreviation/Acronym	Term
ABP	Ambulatory Blood Pressure
ACEi	Angiotensin Converting Enzyme Inhibitor
ADE	Adverse Device Effect
AE	Adverse Event
ARB	Angiotensin Receptor Blocker
CCB	Calcium Channel Blocker
CEC	Clinical Events Committee
CRF	Case Report Form
CTA	Computed Tomography Angiography
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FU	Follow Up
HCTZ	Hydrochlorothiazide
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intention To Treat
MRA	Magnetic Resonance Angiography
MAE	Major Adverse Event
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effect

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