CLINICAL STUDY PROTOCOL

The "RADIANCE-HTN" Study
A study of the ReCor Medical Paradise System in Clinical Hypertension

Protocol Number: CLN 0777

Sponsor: ReCor Medical Incorporation / ReCor Medical BV / ReCor Medical, Ltd.

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Current Version: Version C

Release Date: October 11, 2019

NCT 02649426

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Revision History

Revision Number	Release Date	Description
A	September 21, 2015	Initial Release
A	November 15, 2015	Initial Release- editorial updates
A	December 11, 2015	Initial Release- FDA updates
B	July 13, 2018	Clarification regarding Cross-Over process; addition of revised treatment strategy; Study PI change
C	October 11, 2019	• Addition of 3.5mm balloon size and update to renal artery diameter size eligible for treatment • Clarification of treatment strategy with addition of treatment strategy example figures • Addition of 4 & 5 Year follow-up visits; • Addition of Observational Efficacy endpoints for evaluation of blood pressure at all follow-up timepoints; • Update of company contact information • Update the radiation exposure risk to include the potential teratogenic damage, if pregnant • 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 Purpose	The purpose of the RADIANCE-HTN study is to demonstrate the ability of the Paradise System to effectively reduce systolic daytime ambulatory BP (ABP) in hypertensive subjects. In addition the study is designed to document the safety profile of the Paradise System in all treated subjects.
Study Objective	The objective of the RADIANCE-HTN study is to demonstrate the efficacy and verify the safety of the Paradise System in two distinct populations of hypertensive subjects. Prior to randomization, subjects will be hypertensive in the absence of hypertension medication or despite the presence of a stabilized, single pill, triple, fixed dose antihypertensive medication regimen.
Study Design	RADIANCE-HTN is a randomized, double-blind, sham controlled, 2-cohort study designed to demonstrate efficacy and document the safety of the Paradise Renal Denervation System in two distinct populations of hypertensive subjects.
Patient Population	Two study cohorts will be evaluated. Subjects with essential hypertension controlled on 1 or 2 antihypertensive medications or uncontrolled on 0-2 antihypertensive medications will be included in the RADIANCE Solo cohort while subjects with treatment resistant hypertension on a minimum of 3 antihypertensive medications will be included in the RADIANCE Trio cohort. <u>RADIANCE Solo Cohort</u> After providing informed consent, subjects with uncontrolled (average seated office BP ≥ 140/90 mmHg and < 180/110 mmHg mmHg) or controlled (average seated office BP <140/90 mmHg) essential hypertension and currently prescribed to 1 or 2 antihypertensive medications 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 currently not prescribed to any antihypertensive medication with an average seated office BP ≥ 140/90 mmHg and < 180/110 mmHg will undergo a 4 week run-in period. After 4 weeks, all subjects will undergo a 24 hour ABP measurement. Those subjects whose daytime ABP remains ≥ 135/85 mmHg and <170/105 mmHg, will at a minimum undergo a baseline renal Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) to rule out renal abnormalities and/or significant renal artery stenosis if one is not already available that has been performed within one year prior to consent. In addition, a baseline renal duplex ultrasound is strongly recommended (a duplex image documented within 6 months of consent is also acceptable). 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 renal denervation or blinded control ("sham").* <u>RADIANCE Trio Cohort</u> After providing informed consent, subjects with uncontrolled, treatment resistant hypertension (average seated office BP ≥140/90 mmHg despite at least three antihypertensive drugs of different classes including a diuretic) will have their current hypertensive regimen replaced

	with a single pill, triple, fixed dose antihypertensive combination of a calcium channel blocker (CCB), angiotensin II receptor blocker (ARB), and hydrochlorothiazide diuretic (HCTZ)** to be administered once daily during a 4 week stabilization period. After 4 weeks, all subjects will undergo a 24-hour ABP measurement. Those subjects whose daytime ABP remains ≥ 135/85 mmHg will at a minimum undergo a baseline renal CTA or MRA to rule out renal abnormalities and/or significant renal artery stenosis if not already performed within one year prior to consent. In addition, a baseline renal duplex ultrasound is strongly recommended (a duplex image documented within 6 months of consent is also acceptable). Subjects with a 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 renal denervation or blinded control ("sham").* **For those subjects randomized to blinded control, the renal angiogram will be considered the sham procedure* ***Options include Tribenzor/Sevikar HCT®; Olmesartan 40/HCTZ 25/Amlodipine 10 (Daiichi Sankyo); Exforge HCT®: Valsartan 160/HCTZ 25/Amlodipine 10 (Novartis) or generic Exforge HCT (TEVA Pharmaceuticals). Amlodipine doses may be reduced to 5mg in the event of disabling severe leg edema* *Note: Subjects with uncontrolled, treatment resistant hypertension currently prescribed to Tribenzor/Sevikar HCT or Exforge HCT (including generics) are eligible. Subjects will be followed for a 4 week stabilization period prior to confirming ABP according to the requirements of the protocol.*
Follow-Up Schedule Post Procedure	The Primary Efficacy endpoint will be collected at 2 months post procedure in both cohorts; however, all subjects will be followed for a minimum of 60 months post procedure. Scheduled in-clinic follow-up (FU) visits will occur at 1, 2, 3, 4, 5, 6, 12, 24, 36, 48 and 60 months post procedure. All subjects will have seated office BP measurements taken at each clinic FU and 24-hour ABP measurements will be taken at 2, 6 and 12 months post procedure. Renal duplex ultrasound will be performed at baseline (recommended), 2, 6, 24 and 36 months post procedure and at any other time in the event there is clinical indication of post-denervation renal stenosis. A FU renal CTA or MRA will be performed 12 months after the procedure in all subjects that have been treated with renal denervation.
Blood Pressure Measurements	To limit variability in BP measurements, scheduled in-clinic visits should occur in the morning (preferably between 08:00 and 10:00am). Up to and including the 6 month FU visit, subjects should not take their study-defined antihypertensive medications on the day of the FU but rather bring their medication with them to the visit. Investigational sites may contact the subject before the scheduled visit to remind them. Antihypertensive medications will then be taken during the FU after office BP measurements have been made and, when applicable, after ABP device set up. Home BP measurements will be taken for the 7 days prior to each office FU (requiring a minimum of 18 BP measures to calculate a sustained average over 7 days). BP values recorded during this period will be used to assess any BP safety issues and determine hypertension medication escalation (see below) after the 2 month Primary Endpoint visit.
Randomization	Separate randomization schedules will be generated for the Solo and Trio Cohorts. The Trio randomization will be stratified by beta blocker use. A 1:1 randomization scheme will be used in both cohorts to assign subjects to treatment or blinded control (sham). Randomization will be generated by computer and stratified by center using blocks of small size and treatment permutation. Randomization will occur immediately following the renal angiogram to maintain subject blinding and to allow that subjects may be excluded prior to randomization for reasons of unsuitable renal anatomy.

Blinding	The subjects and all study personnel taking FU BP measurements will be blinded to the randomization. Subjects will complete a blinding assessment[1] prior to hospital discharge and at 2 and 6 months FU. All ABP measurements will be sent to a core lab.
Changes in Anti-hypertensive Medication	For the period of wash-out/run-in (RADIANCE Solo) or stabilization (RADIANCE Trio) 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 antihypertensive drug wash-out per standard Institutional guidelines • In the incidence of a BP emergency (described below) • In the incidence of a clinical event that means a change in medication becomes necessary Following the 2-month Primary Efficacy endpoint visit, all subjects will remain blinded up to the 6 month visit. Between the 2 and 6 month FU visits, pre-defined escalation of antihypertensive medication is strongly recommended to be used in both cohorts. The medication escalation will start at the FU where a sustained elevation (≥ 135 mmHg systolic or ≥ 85 mmHg diastolic) in 7-day home BP measurement is documented and subsequently confirmed by office BP ≥ 140 or ≥ 90 mmHg (if required per Institutional practice). Drugs will be sequentially added in the event BP remains elevated at the current and subsequent FU visit. In the event BP remains <135/85 mmHg, no action is required. Unless medically contraindicated, introduction of each successive antihypertensive medication should occur sequentially in the order indicated below: RADIANCE Solo Cohort • **Step 1**- Add mid dose long acting dihdropyridine CCB (preferentially Amlodipine 5 mg) • **Step 2**- Add full dose of long acting 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 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: Doses are once daily* Following the 6 month FU, subjects will be un-blinded and may have their medications modified per physician's discretion. RADIANCE Trio Cohort (in addition to the single pill, triple fixed dose antihypertensive combination of Tribenzor/Sevikar HCT or Exforge HCT). • **Step 1**- Add Spironolactone (25-50 mg)

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

	• **Step 2**-Add full dose of long acting, cardioselective Beta-1 receptor blocker (preferentially Bisoprolol 10 mg) • **Step 3**- Add full dose of central Alpha 2 receptor agonist (preferentially Clonidine 0.1-0.2 mg, Rilmenidine 1-2mg or Moxonidine 0.2-0.4 mg) • **Step 4**- Add full dose of long-acting Alpha-1 receptor blocker (preferentially slow release Prazosin 5-10 mg or Doxazosin 4-8 mg) *Note: Doses are once daily other than for Clonidine, Rilmenidine or Moxonidine which should be added twice daily at their higher dosages* Following the 6 month FU, subjects will be un-blinded and may have their medications modified per physician's discretion.
Medication changes due to Hypertensive or Hypotensive Emergency	Since the aim of the RADIANCE-HTN study is to determine the effectiveness of renal denervation without medication changes confounding the results, it is intended that baseline hypertensive medication (or lack of it), be maintained through the Primary Efficacy endpoint visit which occurs two months after randomization. However in cases where medication changes are considered medically necessary (e.g. a significant change in BP or adverse events directly related to BP variations or BP medications), medication and/or doses may be adjusted according to the following guidelines: <u>Low BP Action</u> The dosage of study-defined drugs can be reduced temporarily or discontinued permanently for any subjects whose office systolic BP is reduced to <110mmHg with associated signs and symptoms of hypotension or reduced renal perfusion or an increase in plasma creatinine ≥ 30%. The order in which antihypertensive drugs should be discontinued will depend upon the subjects' assigned cohort (Solo or Trio) and the stage that they are within the scheduled FU. 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.). For subjects in the RADIANCE Trio cohort prescribed only to the single pill, fixed dose combination, reducing or stopping the current dose of HCTZ should be a first step with subjects then being switched to a double combination CCB + ARB (Sevikar® or Exforge®). All changes in antihypertensive treatment will be documented and patient BP data will be included as per intention-to-treat. <u>High BP Action</u> Clinical intervention may be required for patients who have clinical adverse events felt to be related to persistent or elevated hypertension at any visit after randomization defined by 7 day home BP ≥ 170 (systolic) or ≥ 105 mmHg (diastolic) and subsequently confirmed by office BP ≥ 180 or ≥ 120 mmHg (if required per Institutional practice). In these circumstances and assuming the subject is post-randomization, the treatment regimen should follow the hypertension medication escalation algorithm as described above. In the event that a hypertensive emergency is documented prior to randomization, the subject will be treated per Institutional guidelines and withdrawn from the study. All changes in antihypertensive treatment will be documented and patient BP data will included as per intention-to-treat.

Cross-Over to Treatment	Following at least 6 months of FU post procedure, subjects assigned to the Control group may cross-over and receive treatment in the event that all of the following conditions are met: • The Primary Efficacy endpoint has been met in that patients' cohort • The DSMB has not stopped the study due to safety concerns or indicated an increased safety risk associated with the treatment • The subject agrees to the procedure • The subject has an ambulatory daytime systolic ABP ≥ 135 and/or diastolic ABP ≥ 85 mmHg In the event of cross-over to treatment, subjects will undergo a cross-over baseline evaluation, including review of key eligibility criteria, prior to the cross-over procedure. Subjects will then be followed at 1, 2, 6, 12, 24, 36, 48 & 60 months post cross-over procedure.
Medication Compliance	Compliance to the anti-hypertensive medication regimen will be assessed in the Trio cohorts by: • HP LC-MS/MS detection of antihypertensive drug metabolite by urine analysis
Primary Efficacy Endpoint	The Primary Efficacy endpoint will be the same in the two cohorts but analyzed separately; reduction in average daytime ambulatory systolic BP from baseline to 2 months post procedure.
Primary Efficacy Endpoint Statistics	The two cohorts will be analyzed independently for all endpoints. 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 separately for the RADIANCE Solo and RADIANCE Trio cohorts, each at a 0.05 alpha level as there is independent interest in conclusions for each cohort separately. For an assumed treatment effect (mean±standard deviation) of 6±12 mmHg, the planned sample size (n=292) will provide 80% power for each cohort based on a two-sided 0.05 alpha and allows for no more than approximately10% of incomplete datasets and/or subjects to be lost to FU between randomization and the 2 month Primary Efficacy endpoint FU.
Secondary Efficacy Endpoints	• Reduction in average 24-hr/night-time ambulatory systolic BP at 2 months post procedure • Reduction in average daytime/24-hr/night-time diastolic BP at 2 months post procedure
Observational Efficacy Assessments	• Reduction in average office systolic/diastolic BP at 2, 6, 12, 24, 36, 48 and 60 months post procedure • Reduction in average daytime/24-hr/night-time ambulatory systolic BP at 6 and 12 months post procedure • Reduction in average daytime/24-hr/night-time ambulatory diastolic BP at 6 and 12 months post procedure • Reduction in average home systolic/diastolic BP at 2, 3, 4, 5 and 6 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)

	• 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) • 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 • Changes in dipper/non-dipper patterns 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 additional antihypertensive drug therapy between 2 and 6 months post procedure • Percentage of subjects without any antihypertensive treatment at 6 and 12 months post procedure in the RADIANCE Solo cohort • Compliance assessed by urine drug level determinations • Change in plasma biomarkers at 2 and 6 months post procedure (Solo cohort only, optional) • Percentage of patients in whom it is possible to deliver complete ablation profile (as determined by individual anatomy)
Safety Assessments	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 13.1). The occurrence rate for <u>all</u> the clinical events defined below will be calculated for each cohort, characterized by the DSMB and compared between and within arms (where applicable) for the duration of the study. In addition, specific events within this list will also be reported as event rates within specific time frames post procedure. Events to be reported any time during the study: • All-cause mortality • Hypertensive emergency resulting in hospitalization • Hypotensive emergency resulting in hospitalization • Hospitalization for heart failure • Stroke, transient ischemic attack, cerebrovascular accident • Acute myocardial infarction (STEMI/non-STEMI) • Any coronary revascularization • End stage renal disease, the need for permanent renal replacement therapy (i.e. the need for dialysis); doubling of plasma creatinine • Any renal artery complication requiring intervention (e.g. dissection; perforation) • Major access site complications requiring intervention • Significant embolic events resulting in end organ damage • Procedure-related pain lasting for > 2 days • Acute renal injury, defined as: o Increase in plasma/serum creatinine by ≥ 0.3 mg/dl (≥26.5 µmol/l) within 48hrs of the procedure or, o Increase in serum/plasma creatinine to ≥1.5 times baseline known to have occurred during 7 days post procedure or, o Urine volume <0.5 ml/kg/h for 6 hours

	• Significant (>50%) and severe (>75%)[2] new onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA • Need for renal artery angioplasty or stenting *In addition*, these specific events will also be reported as 1 month post procedure event rates: • Any renal artery complication requiring intervention (e.g. dissection; perforation) • Major access site complications requiring intervention • Significant embolic events resulting in end organ damage • Procedure-related pain lasting for > 2 days • Acute renal injury, defined as: o Increase in plasma/serum creatinine by ≥ 0.3 mg/dl (≥26.5 μmol/l) within 48hrs of the procedure or, o Increase in serum/plasma creatinine to ≥1.5 times baseline known to have occurred during 7 days post procedure or o Urine volume <0.5 ml/kg/h for 6 hours *In addition*, these specific events will also be reported as 6, 24 & 36 month post procedure event rates: • Significant (>50%) and severe (>75%) new onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA • Need for renal artery angioplasty or stenting *In addition*, these events will be also reported as 12 months post procedure event rates: • Significant (>50%) and severe (> 75%) new onset renal stenosis as diagnosed by study-defined renal CTA/MRA • Need for renal artery angioplasty or stenting
Safety Design Justification	This is the first randomized, blinded study evaluating the Paradise ultrasound technology and as such cardiovascular, device and procedural event rates are important determinants of the safety profile of the system. For this reason no pre-specified endpoint has been defined. To ensure that subjects are not inappropriately exposed to an increased risk of cardiovascular events including stroke and/or renal stenosis, the following measures have been included: • Drug discontinuation in the RADIANCE Solo cohort will occur in line with accepted Institutional guidelines for a subjects' current medication and subjects' whose baseline eligibility systolic/diastolic office BP is ≥180/110 mmHg or baseline daytime ABP is ≥170/105 mmHg are excluded • Drug discontinuation in the RADIANCE Solo cohort is limited to a short period of approximately 3 months during which timeframe subjects are a low risk of any CV event off treatment[3]

[2] Hirsch A, et al., ACC/AHA 2005 Practice Guidelines for the management of peripheral arterial disease (lower extremity, renal, mesenteric and abdominal aortic) 2006. Circulation e465-e655

[3] DeFelice, A et al., 2008. The risks associated with short-term placebo-controlled antihypertensive clinical trials: a descriptive meta-analysis. J Hum Hypertens. 22: 659-688

	• All subjects will be provided with home BP monitoring devices from the point of a) drug discontinuation or run-in (RADIANCE Solo cohort) or b) initiation of fixed dose triple combination therapy (RADIANCE Trio Cohort) • Subjects whose average home BP increases to ≥170 mmHg systolic or ≥105 mmHg diastolic and who have clinical events considered to be related to persistent or elevated hypertension pre-randomization such that a change in medication is necessitated, will be excluded • Subjects whose average home BP increases to ≥170 mmHg systolic or ≥105 mmHg diastolic, post randomization will be eligible to have their anti-hypertensive medication restarted or modified as needed • Subjects in the RADIANCE Solo cohort will have anti-hypertensive drug therapy initiated immediately following the 2 month FU if needed • Non-invasive imaging will be required for all subjects at baseline (CTA/MRA at a minimum), the 2 and 6 month FUs (duplex ultrasound) and for all treated subjects at the 12 month FU (CTA/MRA) and the 24 and 36 month FUs (duplex ultrasound)
Additional Safety Assessments	• Level of post-procedural pain as determined by the use of a Visual Analog Scale • Incidence of severe procedural pain defined as a score of ≥ 8 on the Visual Analog Scale • Incidence of new onset orthostatic hypotension post procedure • Change (reductions) from baseline in mean eGFR at 2, 6, & 12 months post-procedure • Change (increases) from baseline in mean plasma creatinine at 2, 6 & 12 months post-procedure
Pre-specified cohorts for analysis	Post-hoc evaluations of efficacy will be evaluated in specific subgroups including but not limited to: • Gender • Ethnicity • Age • Baseline ABP • BMI • Geography • Number of ablations • Renal anatomy
Overall Sample Size	64 randomized subjects per arm 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, 80% power and a 2-sided 0.05 alpha. The estimated minimum sample size therefore to demonstrate efficacy is 128 subjects in each cohort. To account for an approximate 10% rate of premature withdrawal or failure to reach the primary end point measure, up to 146 subjects will be recruited and randomized into each cohort for a total sample size of 292 randomized subjects of which 146 will be treated.
Study Geographies	RADIANCE-HTN will be conducted at up to 40 clinical investigational sites in the USA and up to 40 sites outside the USA.
Study Duration	The expected duration, from enrollment to study closure, will be approximately 120 months.

Overall Subject Selection	Subjects following the indications/contraindications for use of the Paradise System with a documented history of essential hypertension, 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. Minor differences in inclusion/exclusion criteria exist between the RADIANCE Solo and RADIANCE Trio cohorts reflecting the different stage in hypertension progression for each group. Specific differences are shown in bold.

Inclusion Criteria: Solo Cohort	Male and female subjects who meet the following criteria should be given consideration for inclusion in the Solo Cohort:
	• Appropriately signed and dated informed consent
	• Age ≥18 and ≤75 years at time of consent
	• Documented history of essential hypertension
	• Either,
	  o Average seated office BP < 180/110 mmHg at screening visit (V0) while on a stable regimen of 1 or 2 antihypertensive medications for at least 4 weeks prior to consent or,
	  o Average seated office BP ≥ 140/90 mmHg <180/110 mmHg despite lifestyle measures on no antihypertensive medications
	• Documented daytime ABP ≥ 135/85 mmHg and < 170/105 mmHg 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) renal imaging)
	• Able and willing to comply with all study procedures

Exclusion Criteria: Solo Cohort	Subjects who meet any of the following criteria will be excluded from the Solo Cohort:
	• Renal artery anatomy on either side, ineligible for treatment including:
	  o Main renal artery diameter < 4 mm and > 8 mm
	  o Main renal artery length < 25 mm
	  o A single functioning kidney
	  o Presence of abnormal kidney (or secreting adrenal) tumors
	  o Renal artery with aneurysm
	  o Pre-existing renal stent or history of renal artery angioplasty
	  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 ≥ 2mm <4 mm and > 8 mm*
	• 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%)
	• 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 (myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV)
	• Documented confirmed episode(s) of stable or unstable angina

	• **Documented repeat (>1) hospitalization for hypertensive crisis within the prior 12 months** • 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 • 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 • 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 (e.g. night shift workers) • Pregnant, nursing or planning to become pregnant (negative pregnancy test required, documented within a maximum of 7 days prior to procedure for all women of child bearing potential. Documentation of effective contraception is also required for women of child bearing potential) • Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable) ** This 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*
Inclusion Criteria: Trio Cohort	Male and female subjects who meet the following criteria should be given consideration for inclusion in the Trio Cohort: • Appropriately signed and dated informed consent • Age ≥18 and ≤75 years at time of consent • Documented history of hypertension • Average seated office BP ≥ 140/90 mmHg at screening visit (V0) while on a stable regimen of at least 3 antihypertensive medications of different classes including a diuretic for at least 4 weeks prior to consent • Documented daytime ABP ≥ 135/85 mmHg after 4-week stabilization 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) renal imaging) • Able and willing to comply with all study procedures
Exclusion Criteria: Trio Cohort	Subjects who meet any of the following criteria will be excluded from the Trio Cohort: • Renal artery anatomy on either side, ineligible for treatment including: o Main renal artery diameter < 3 mm and > 8 mm o Main renal treatable artery length < 20 mm (may include proximal branching) o A single functioning kidney o Presence of abnormal kidney (or secreting adrenal) 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

	○ Fibromuscular disease of the renal arteries ○ Presence of renal artery stenosis of any origin ≥ 30% ○ Accessory arteries with diameter ≥2 mm < 3 mm or > 8 mm* • Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter • Evidence of active infection within 7 days of procedure • **Secondary hypertension not including sleep apnea (documented through clinical work up within the 12 months prior to consent- see protocol body for details)** • Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma Hb1Ac ≥ 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) **within 3 months prior to consent** • Any history of severe cardiovascular event (e.g. myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV) **within 3 months prior to consent** • Documented repeat (>1) hospitalization for hypertensive crisis **within the prior 3 months** • Documented confirmed episode(s) of unstable angina **within 3 months prior to consent** • **Documented intolerance or contraindication for any of the antihypertensive drugs prescribed as a requirement of the study protocol** • Prescribed to any standard anti-hypertensive CV medication (**other than beta blockers**) for other chronic conditions (e.g. ischemic heart disease) such that discontinuation might pose serious risk to health • 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 • 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 (e.g. night shift workers) • Pregnant, nursing or planning to become pregnant (documented negative pregnancy test required documented within a maximum of 7 days prior to procedure for all women of child bearing potential. Documentation of effective contraception is also required for women of child bearing potential) • Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable) ** This 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-HTN 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 independent physicians.
Ethics	The study will be conducted in accordance with the declaration of Helsinki, ISO 14155:2011, FDA 21 CFR parts 50, 54, 56, 812 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. Uncontrolled hypertension may be caused by multiple factors including inadequate or inappropriate treatment, poor medication adherence[vi,vii] and in a 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] Resistant hypertension has been estimated to affect 15% to 30% of participants in clinical trials of antihypertensive medication and 5% to 30% of patients in clinical practice.[viii] While the specific benefits of treating resistant hypertension compared with more easily controlled hypertension are not known, it is well-established that hypertension control as a means to prevent cardiovascular morbidity and mortality provides substantial clinical and economic benefit.[ix]

2.2. *Other Therapeutic Options*

Currently therapeutic options outside the use of standard classes of antihypertensive medication are limited for patients with resistant hypertension.[x] Novel antihypertensive drug classes are being explored that may enhance options for patients resistant to multiple drug treatment, including direct renin inhibition (e.g., Aliskiren), centrally-acting sympatholytics (e.g., Clonidine & Rilmenidine), and selective endothelin receptor antagonists. However, the limitations of purely pharmacologic therapy for patients with resistant hypertension (e.g., treatment failure in a significant subset of patients, adherence challenges, side effects, and concerns regarding polypharmacy), have prompted the exploration of interventional approaches to provide complementary therapeutic tools.

2.3. *Role of the Sympathetic Nervous System*

The etiology of resistant hypertension is likely multifactorial. However, 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.[xi,xii] 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.[xiii,xiv] 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.[xv] 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.[xvi] 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.[xvii,xviii,xix,xx]

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® 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. Subsequent to development of the original Symplicity Catheter System, other RF systems using the same general model of energy delivery have been developed including primarily the Vessix Renal Denervation System (Vessix Vascular, Inc. Laguna Hills, VA, USA) which consists of a non-compliant balloon catheter with bipolar electrodes mounted on the exterior of the balloon and the EnligHTN™ multi electrode Renal denervation system (St Jude Medical, St Paul, MN, USA). The ReCor Medical Paradise renal denervation system is differentiated from these 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. ***Prior Renal Denervation Clinical Evidence***

The primary clinical data supporting percutaneous RF renal denervation comes from studies evaluating the performance of the Symplicity Catheter System[xvii,xviii,xix,xxi,] although both the Vessix[xxii] and EnligHTN[xxiii] Systems have some level of clinical evidence supporting them.

2.4.1. **Symplicity HTN-1 and HTN-2**

The initial Symplicity study (HTN-1) was a 50 patient, un-blinded, single arm, observational study designed to demonstrate proof-of-concept and was conducted at five centers in Europe and Australia.[xvii] The results from HTN-1 were based on average office BP measurements which were shown to be significantly lowered at 1, 3, 6, 9 and 12 months post treatment with a range of systolic BP drops from -14 mmHg at 1 month to -27 mmHg at 12 months. A follow-up publication on the long-term, 3-year data from the treated patients demonstrated that the treatment effect appeared to be sustained over time.[xxiv] Safety data supported that the procedure was low risk with only one renal artery dissection reported.

The compelling data from the HTN-1 study was followed quickly by results from HTN-2 which was a non-blinded, randomized, placebo- controlled evaluation of the effect of the Symplicity catheter in

resistant hypertensive patients. The study enrolled 106 patients (52 randomized to renal denervation and 54 to control) and the patients were followed for 6 and 12 months. In line with the early data from HTN-1, HTN-2 also documented substantial drops in office BP at 6 and 12 months (-32/-12 mmHg and -28/-10 mmHg in the treatment group respectively) while the control group showed a small increase in BP at 6 months (+7/+1 mmHg).[xviii]. In addition, Control patients who elected to cross-over after 6 months, also demonstrated significant drops of office BP following 6 months of treatment (-24/-8 mmHg).[xix] However, despite the supposedly effective data being reported from the HTN-1 and 2 trials plus evidence from multiple observational studies including the large Global Symplicity Registry,[xxv] concerns were being voiced related to the strength of the data including the unprecedented size of the documented office BP drops, the lack of strict control over criteria for resistant hypertension, limited ambulatory BP (ABP) evidence and absence of blinding and sham control.[xxvi,xxvii]

2.4.2. **Symplicity HTN-3**

In contrast to HTN-1 and HTN-2, the Symplicity HTN-3 trial was a randomized, blinded and sham-controlled safety and efficacy evaluation of the Symplicity catheter conducted at 88 US clinical centers. A total of 535 patients whose baseline office systolic BP was ≥160 mmHg despite stable 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.[xxviii] 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.[xxix] Despite the lack of significant effectiveness of the treatment versus a sham procedure, 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 early data from HTN-1 and 2 and has resulted in substantial discussions related to the appropriate design and implementation of future renal denervation clinical trials.[xxx,xxxi]

2.4.3. **The Renal Denervation for Hypertension (DENERHTN) Trial**

Recently a French Ministry of Health-sponsored study of the Symplicity Catheter (DENERHTN) was published in Lancet[xxxii] evaluating the effect of RF renal denervation in 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. Approximately half of 1416 screened patients were excluded due to the documented presence of clinical causes of secondary hypertension. Patients were initially followed for 6 months with monthly in-office visits and monitoring of home BP. A predefined antihypertensive medication escalation protocol was in place for both groups so that drug burden could be evaluated at 6 months post randomization and to ensure that patients were not allowed to remain hypertensive for extended periods of time. 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. DENERHTN is currently the only blinded, placebo-controlled, evidence demonstrating significant effect of renal denervation in resistant hypertension and its design is likely to provide important insight into key factors to be considered when designing future evaluations of renal denervation.

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[xxxiii]. Subsequently, two multi-center, ReCor Medical Inc. sponsored post-market evaluations (the REALISE and ACHIEVE studies) were initiated in 2012, and 2013, respectively.

3.2. *The REDUCE Study*

Patients enrolled in the REDUCE study were diagnosed with resistant hypertension as defined by the 2007 European Society of Hypertension and the European Society of Cardiology, with a minimum BP of 140/90 mmHg (office), 135/85 mmHg (home) and 130/80 mmHg (ambulatory) despite being treated with at least three antihypertensive medications including a diuretic. Patients under the age of 18 years, pregnant, allergic to contrast media, or with any known cause of secondary hypertension were excluded. A CT-scan was performed at screening to further exclude patients with vascular abnormalities (including renal artery stenosis and iliac or femoral artery stenosis precluding insertion of the Paradise catheter) or not meeting the anatomical criteria (renal artery of more than 20 mm in length and 4 mm in diameter).

Fifteen patients with resistant hypertension underwent renal denervation in the REDUCE study. All patients met the ESH-ESC criteria for resistant hypertension at baseline. Patients took, on average, 4.1 antihypertensive medications, with 100% receiving diuretics, 87% calcium-channel blockers, and 87[% angiotensin-converting enzyme inhibitors. The mean age of enrolled patients was 52 years; 40% were male. Baseline co-morbidities and cardiovascular risk factors included diabetes (20%), history of angina/ myocardial infarction (33%), history of stroke (20%) and one patient had a history of obstructive sleep apnea. The average office blood pressure at baseline was 182±22/110±15 mmHg and average baseline 24-hour ambulatory blood pressure was 173±19/102±16 mmHg. A 12-French treatment catheter with 8 mm balloon was used for the first three cases, while the subsequent 12 subjects were treated with a 6 French catheter with either a 6 mm or 8 mm balloon. Up to three ultrasound emissions were delivered in each renal artery at variable energies and with variable cooling flow rate. The majority of emissions were for 50 seconds (range 14-55). Eight patients were treated with low cooling flow of either 8ml/minute (n=5) or 5 ml/minute (n=3). Of those patients treated with low cooling flow, two developed clinically significant renal artery stenosis noted at their 6-month FU visit, requiring angioplasty and stenting. One additional patient developed renal artery stenosis beyond the 6-month visit which was treated with angioplasty. The stenoses were attributed to inadequate cooling of the renal arterial wall. Accordingly, the cooling flow rate was increased to 41-50 ml/minute for all subsequent procedures in REDUCE, as well as for all future clinical use of the Paradise System

Pretreatment, mean office systolic BP was 182±22 mmHg (n=15), and mean 24-hour ambulatory systolic BP was 173±19 mmHg (n=13). Following bilateral treatment with the Paradise System, reductions in office systolic BP were observed by 3 months (-27.4±26.2) and sustained through 6 and 12 months, (-32.7 ±27.3 at 6 months and -28.9±32.2 at 12 months). Similarly, meaningful reductions in ambulatory systolic BP were observed at 3 months (-9.7±15.2) 6 months (-13.6±14.8) and 12 months (-6.9±15.5).

Pain (back; abdominal; groin) associated with the procedure was reported in 9/15 patients (60%). A total of five device-related events requiring intervention were reported: three cases of stenosis discussed above; one case of procedural renal artery dissection caused by a guide wire; and one case of significant vasospasm requiring angioplasty. One patient experienced a hypertensive crisis requiring hospitalization within 30 days of the procedure. The patient was stabilized with medication and discharged within 24 hours with no further reports of hypertensive crisis.

In summary the REDUCE study was designed to document the safety and effectiveness of the Paradise System in the setting of a first-in-man feasibility study. There have been significant changes implemented to the Paradise System based on the REDUCE experience.

3.3. *The REALISE Study*

The REALISE Study was designed as an adjunct confirmatory clinical study based on the REDUCE protocol to further evaluate the Paradise System. The study was a single-arm, open label prospective study conducted in France at two clinical sites to evaluate the Paradise System in patients with moderate resistant hypertension defined by the 2007 ESH/ESC guidelines. Per the guidelines, patients were required to have a baseline office BP >140/90 mmHg despite the use of a minimum of 3 antihypertensive medications, including a diuretic on maximally tolerated doses. All patients enrolled in the study were managed by a multi-disciplinary team which included a hypertension specialist. The majority of patients were on 5 anti-hypertensive medications at baseline, and 70% of patients were taking Spironolactone at baseline.

Enrollment in the REALISE study was completed in March 2014. One year FU on all patients was completed on March 21, 2015. The mean age of enrolled patients was 54 years; 70% were males. Baseline comorbidities and cardiovascular risk factors included type II diabetes mellitus (45%), history of peripheral vascular disease (35%), history of stroke (30%), history of myocardial infarction (30%), history of obstructive sleep apnea (30%), and prior renal denervation (5%). The mean office systolic BP at baseline was 168±19 mmHg (n=19), and mean ambulatory systolic BP at baseline was 157±14 mmHg (n=20). Following bilateral treatment with the Paradise System, reductions in office systolic BP were observed by 3 months (-7.4±28.2) and sustained through 6 and 12 months (-10.5±33.6 at 6 months, and -16.6±27.2 at 12 months). Similarly, meaningful reductions in ambulatory systolic BP were observed at 6 months (-7.8±17.4) and 12 months (-5.2±12.7. In addition, post treatment, the mean antihypertension medication burden decreased from 5.4 to 4.4 with an overall reduction in medication burden of 21%.

System related safety events were minimal with none requiring intervention or hospitalization. These included back pain (n=9); non-specific abdominal pain (n=1), mild access related vascular injury (n=1) and minor intimal dissection in the left renal artery during the procedure that did not require intervention (n=1). Safety events beyond 30 days included renal complications defined as worsening pre-existing renal failure (n=2), thromboembolic event (stroke 5 months post procedure, n=1) and death (11 months post procedure due to pneumococcal meningitis, n=1). There have been no reports of new onset renal artery stenosis.

In summary, The REALISE study demonstrated a reduction in office and ABP sustained through 12 months following treatment with the Paradise System in patients with moderate resistant hypertension despite optimal medical management, including Spironolactone, in the majority of patients.

3.4. *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.

3.5. *The RADIANCE-HTN Study[xxxiv] (on-going)*

The SOLO cohort of the RADIANCE-HTN Study completed recruitment on December 28th 2017. 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 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)[xxxv]. No major adverse events have been reported in either the Treatment or Control arms in the RADIANCE-HTN SOLO Cohort to date.

4. The Paradise® Renal Denervation System

4.1. *Device System Overview*

The ReCor Medical Paradise® 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 serial number, from the Catheter to the Generator as well as the transfer of electrical energy during the procedure

Table 4.1-1, identifies the components of the Paradise System and their basic attributes.

Table 4.1-1: 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-CC-02	Paradise Cartridge	Yes	No	No
PRDS-CT-02	Paradise Connection Cable	Yes	No	No

4.2. *Main Components of the Paradise System*

4.2.1. **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 4.2-1 & 4.2-2) is available in 3.5, 6, 7 and 8 mm balloon sizes.

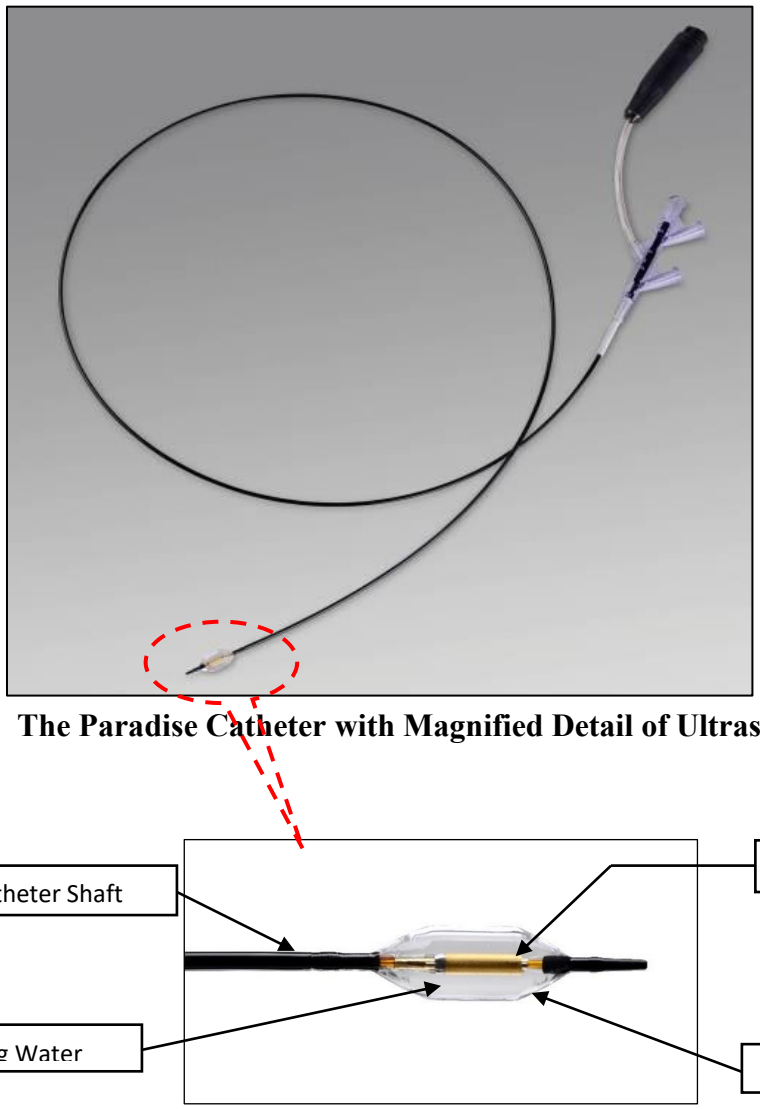
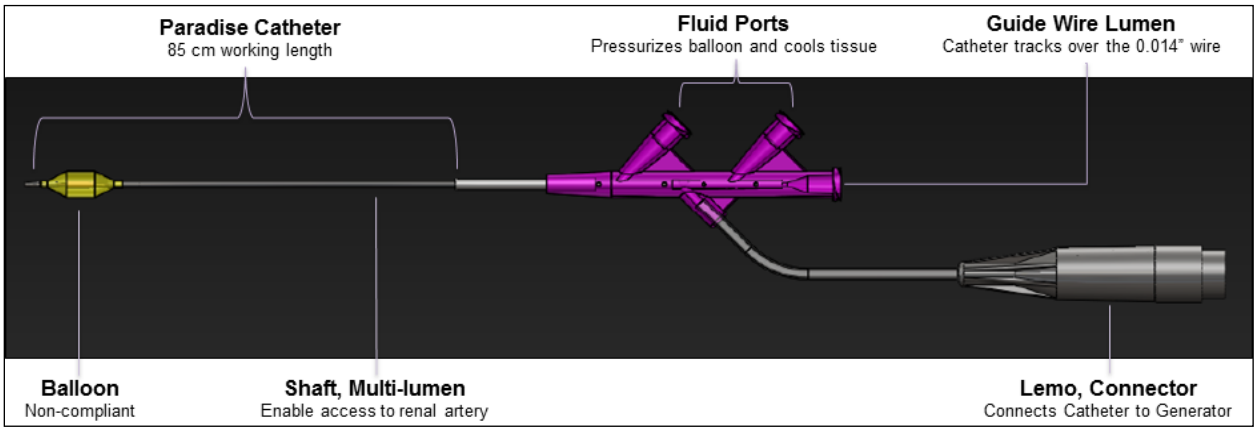


Figure 4.2-1: The Paradise Catheter with Magnified Detail of Ultrasound Source

Figure 4.22-2. 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.

4.2.2. 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 denervates the renal artery nerves safely and effectively.

Figure 4.2-3 below illustrates the Paradise Generator and accessories with its components identified.

Figure 4.2-3. 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.

4.2.3. 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 4.2-4 illustrates the Paradise Cartridge.

Figure 4.2-4. Paradise Cartridge Diagram

The Paradise Connection Cable (as shown in Figure 4.2-5) provides the electrical connectivity between the Generator and the Catheter.

Figure 4.2-5. Paradise Connection Cable Diagram

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

4.3.1. Sterile Water

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

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

4.3.2. 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. The following Guide Catheters are recommended for use:

- 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-Top RDC (7 or 8 French; 55 cm)
- Terumo Destination® Guiding Sheath (6 French; 45 cm)

The following Guide Catheters should not be used:

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

4.3.3. Guide Wires

Any 0.014", 190 cm, heavy or middle weight commercially available guide wire may be used with the Paradise Catheter. The following guide wires are specifically recommended for use:

- Abbott Vascular Balance Middleweight (BMW)
- Abbott Vascular Balance Heavyweight (BHW)
- Cordis ATW
- Biotronik Galeo M
- Abbott Spartacore 14

Note: Guidewires with floppy distal tips are not recommended.

4.3.4. Hemostasis Valve

A non-threading hemostasis valve is necessary to ensure appropriate catheter sterile water flow. The following hemostasis valve is required for optimal Paradise System function:

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

4.4. *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.

4.5. *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.

5. RADIANCE Study Purpose and Objectives

5.1. *Study Purpose*

The purpose of the RADIANCE-HTN study is to demonstrate the ability of the ReCor Medical Paradise System to effectively reduce systolic daytime ABP in hypertensive subjects. In addition, the study is designed to document the safety profile of the Paradise System in all treated subjects

5.2. *Study Objectives*

The objective of the RADIANCE-HTN study is to demonstrate the efficacy and verify the safety of the Paradise System in two distinct populations of hypertensive subjects. Prior to randomization, subjects will be hypertensive in the absence of hypertension medication or despite the presence of a stabilized, single pill, triple, fixed dose antihypertensive medication regimen. Study endpoints have been formulated to support these objectives.

5.2.1. **Primary Efficacy Endpoint**

The Primary Efficacy endpoint will be the same in the two cohorts but analyzed separately; reduction in average daytime ambulatory systolic BP at 2 months post procedure.

5.2.2. **Secondary Efficacy Endpoint**

The Secondary efficacy endpoints will be:

- Reduction in average 24-hr/night-time ambulatory systolic BP at 2 months post procedure
- Reduction in average daytime/24-hr/night-time diastolic BP at 2 months post procedure

5.2.3. **Observational Efficacy Assessments**

The following observational assessments will also be documented:

- Reduction in average office systolic/diastolic BP at 2, 6, 12, 24, 36, 48 & 60 months post procedure
- Reduction in average daytime/24-hr/night-time ambulatory systolic BP at 6 and 12 months post procedure
- Reduction in average daytime/24-hr/night-time ambulatory diastolic BP at 6 and 12 months post procedure
- Reduction in average home systolic/diastolic BP at 2, 3, 4, 5 and 6 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)
- 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)
- 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
- Changes in dipper/non-dipper patterns 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 additional antihypertensive drug therapy between 2 and 6 months post procedure
- Percentage of subjects without any antihypertensive treatment at 6 and 12 months post procedure in the RADIANCE Solo cohort
- Compliance assessed by urine drug level determinations (Trio Cohort)
- Change in plasma biomarkers at 2 and 6 months post procedure (Solo Cohort, optional)
- Percentage of patients in whom it is possible to deliver complete ablation profile (as determined by individual anatomy)

5.3. *Safety Assessments*

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 13.1).

The occurrence rate for all the clinical events defined below will be calculated for each cohort, characterized by the DSMB and compared between and within arms (where applicable) for the duration of the study. In addition, specific events within this list will also be reported as event rates within specific time frames post procedure.

Events to be reported any time during the study:

- All-cause mortality
- Hypertensive emergency resulting in hospitalization
- Hypotensive emergency resulting in hospitalization
- Hospitalization for heart failure
- Stroke, transient ischemic attack, cerebrovascular accident
- Acute myocardial infarction (STEMI/non-STEMI)
- Any coronary revascularization
- End stage renal disease, the need for permanent renal replacement therapy (i.e. the need for dialysis); doubling of plasma creatinine
- Any renal artery complication requiring intervention (e.g. dissection; perforation)
- Major access site complications requiring intervention
- Significant embolic events resulting in end organ damage
- Procedure-related pain lasting for > 2 days
- Acute renal injury, defined as:
    - Increase in plasma/serum creatinine by ≥ 0.3 mg/dl (≥26.5 µmol/l) within 48hrs of the procedure or,
    - Increase in serum/plasma creatinine to ≥1.5 times baseline known to have occurred during 7 days post procedure or
    - Urine volume <0.5 ml/kg/h for 6 hours
- Significant (>50%) and severe (>75%)[4] new onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA

[4] Hirsch A, et al., ACC/AHA 2005 Practice Guidelines for the management of peripheral arterial disease (lower extremity, renal, mesenteric and abdominal aortic) 2006. Circulation e465-e655

- Need for renal artery angioplasty or stenting

In addition, these specific events will also be reported as 1 month post procedure event rates:

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

In addition, these specific events will also be reported as 6, 24 & 36 months post procedure event rates:

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

In addition, these specific events will be also reported as 12 months post procedure event rates:

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

5.3.1. Additional Safety Assessments

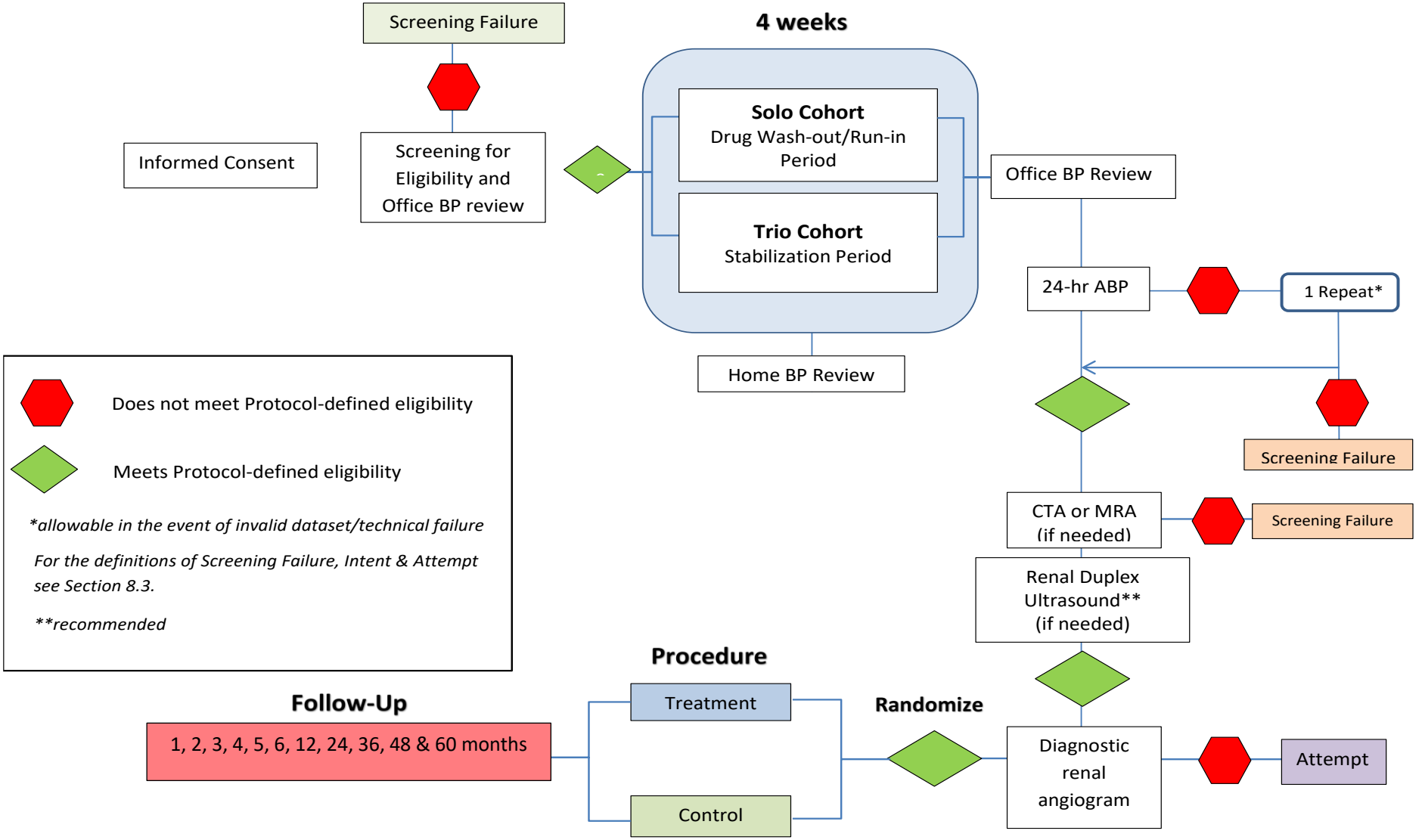
The following observational assessments will also be documented:

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

6. Design

The RADIANCE-HTN Study is a multi-center, randomized, double-blind, sham controlled, 2-cohort study designed to demonstrate efficacy and document safety of the Paradise System in two distinct populations of hypertensive subjects. The study will be conducted in up to 40 clinical investigational sites in the USA and up to 40 sites outside of the USA.

Figure 5.3-1: RADIANCE-HTN Study Design



6.1. *Duration*

The RADIANCE-HTN Study will include up to 292 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 120 months. Figure 5.3-1 documents the study flow.

6.2. *Treatment and Control Assignment*

The RADIANCE-HTN Study is a randomized study requiring treatment and blinded control assignments in both the Solo and Trio Cohorts. Subjects meeting all the inclusion criteria and none of the exclusion criteria will be assigned in a 1:1 (Treatment: Blinded Control) scheme. Subjects will be considered to count towards the enrollment ceiling at the point of randomization independent of whether they undergo a successful procedure or not (see Section 8.3 for subject classifications).

6.3. *Blinding*

All subjects will be blinded up to the 6 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. Other methods such as standardization of length of time spent in cath lab for blinded controls, removal of clocks in recovery room and prevention of contact between subjects treated on the same day may be considered.
- A blinding index[xxxvi] 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 and 6 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 pre-discharge evaluation be completed by un-blinded site personnel aware of the details of the procedure. 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 un-blinded at the 6-month follow-up. Blinding is further defined in the RADIANCE-HTN Blinding & Emergency Un-blinding Process Document (CLN-0029).

The Sponsor will be blinded to the Primary Efficacy Endpoint data which will be handled directly through the ABP core lab and independent statistician. Due to the nature of their support role, Sponsor representatives may be un-blinded to a limited number of randomization due to presence at Procedures and/or during monitoring (see Sections 17.4 and 18.1). 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.

6.4. *Cross-Over to Treatment*

Following at least 6 months of FU post procedure, subjects randomized to the Control group may cross-over and receive treatment in the event that all of the following conditions are met:

- The Primary Efficacy endpoint has been met in that patients' cohort

- The DSMB has not stopped the study due to safety concerns or indicated an increased safety risk associated with the treatment
- The subject has an ambulatory daytime systolic BP ≥ 135 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 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 (negative pregnancy test required, documented within a maximum of 7 days prior to procedure for all women of child bearing potential).

*Up to 2 ABPM recordings may be performed to confirm eligibility with no more than 6 weeks between recordings.
** Results from the tests performed as part of the most recent study follow-up visits may be used unless there are major changes to the patient condition or treatment.

Sites will be informed by the Sponsor at the point that a cross-over becomes an option. Subjects that cross-over to treatment will be followed according to the cross-over visit schedule (see Table 9.1-2).

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

6.5. *Sample Size Rationale and Statistical Power*

The sample size for the study is based on a desire to compare randomized groups separately for each cohort at the point of the Primary Efficacy Endpoint. Calculations are based on evaluating the treatment versus control groups for 1) the RADIANCE Solo and 2) RADIANCE Trio cohorts) independently.

Statistical analyses will be performed separately for the RADIANCE Solo and RADIANCE Trio cohorts, each at a two-sided 0.05 alpha level as there is independent interest in conclusions for each cohort separately. Conservatively, sample size calculations are based on a two-sample t-test. The planned analysis with the adjustment for baseline should provide additional power beyond this, but the precise level depends on the correlation of the baseline value with the reduction during FU. Based on a two-sample t-test, for an assumed mean±standard deviation difference of 6±12 mmHg, a planned evaluable sample size of 128 subjects per cohort will

provide 80% power. These calculations can be confirmed with the following SAS System (version 9.3) code:

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

To account for the loss of power due to missing data at the 2 month FU visit, an approximate 10% inflation is used so the total randomized per cohort is planned at 146 subjects, or 292 total.

6.6. *Justification for the Study Design*

The recent 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. Subsequent evaluation of the data, indicate that one major confounder of the outcome may have been patient compliance to the drug regimen, a complex phenomenon well documented in the pharma literature.[vi,vii] There is also evidence that despite the initial belief that the severely resistant hypertensive patient population may be the appropriate target for renal denervation, the pathophysiology of these patients may not make them amenable to any attempts to reduce BP particularly because of the incidence of endothelial dysfunction, inflammation and extreme arterial stiffness.[xxxvii],[xxxviii] For these reasons, and understanding that blood pressure is a continuous variable, RADIANCE-HTN has been designed to evaluate the effect of renal denervation in two valid but distinct patient cohorts that may respond differently to renal denervation.

6.6.1. **RADIANCE Solo Cohort Justification**

The "RADIANCE Solo" cohort which will be treated in the absence of any antihypertensive drugs will allow the evaluation of renal denervation without the confounding influence of drugs either from a pharmacological or patient compliance perspective. Moreover, these patients tend to be younger with higher sympathetic nervous system activity than patients with more severe resistant hypertension[xxxix] suggesting that they may be more susceptible to renal denervation. Additionally, the arterial wall in younger, less severely hypertensive patients may be more responsive to renal denervation-induced changes in sympathetic tone since vascular remodelling is still in a reversible state. Indeed, the high prevalence of target organ damage in patients with resistant hypertension, including renal fibrosis and vascular stiffness which are difficult to reverse, renders BP control difficult to achieve whatever methods are used. Finally, the potential that pill burden may be reduced subsequent to successful renal denervation, might be of particular benefit in this younger population The evaluation of antihypertensive therapy in a "drug-free" cohort has precedence in the pharmaceutical industry and the patient population has been defined to minimize risk of cardiovascular events including stroke. The time that RADIANCE Solo cohort patients will be taken off their antihypertensive medications is limited specifically in line with the short-term study designs typically used to evaluate new antihypertensive therapy against placebo control. On the basis of the Placebo in Hypertension Adverse Reaction Meta-analysis Project,[xl] the risks associated with such placebo-controlled study designs appear justified particularly in light of the positive safety profile (immediate, mid-

term and long-term vascular safety) so far documented from more than 3000 renal denervation procedures performed world-wide with RF catheters and more than 200 procedures with the Paradise Catheter.

6.6.2. **RADIANCE Trio Cohort Justification**

The "RADIANCE Trio" cohort will allow evaluation of the effect of renal denervation in the more traditional resistant hypertension patients (per the definition of at least 3 antihypertensive drugs including a diuretic) but with the added advantages of using a single, pill, fixed combination triple combination of a CCB, ARB and hydrochlorothiazide diuretic (HCTZ). Since there remains a real barrier to diagnosing resistant hypertension because of 1) the failure of healthcare providers to appropriately increase and/or change a patients therapeutic regimen (known as clinical or therapeutic inertia[xli]) and 2) a well-documented inverse relationship between adherence and the number of antihypertensive drugs that a patient is required to take[xlii,xliii] there is a real possibility that unless appropriately managed, patients in the RADIANCE Trio cohort may have poorly controlled rather than resistant hypertension. The use of a single-pill triple-combination antihypertensive therapy is likely to improve adherence and hence increase the probability of documenting controlled BP in patients who are not actually resistant. While this may require a larger screening population in order to enroll the required number of subjects, it is likely that the population that will be more homogenous and with a higher probability of being actually uncontrolled on three antihypertensive drugs. There is some evidence that subjects with increased incidence of endothelial dysfunction, inflammation and extreme arterial stiffness may not be amenable to renal denervation control of BP.[xxxvi,xxxvii] With that in mind, the inclusion/exclusion criteria of the study have been designed to minimize inclusion of subjects with substantial arterial stiffness.

The study design aims to establish that within 2 months of randomization, either one or both, of these subject cohorts will respond to renal denervation with a reduction in daytime ABP that is significantly different between treated and blinded control subjects (sham). The use of ABP for the efficacy endpoints is designed to reduce the placebo effect and variability often associated with the use of office BP. The study design of evaluating multiple subject cohorts within the realms of a single study has general precedence in the pharmaceutical industry where it is frequently used to test multiple drug combinations and/or doses within a single study.[xliv] In a similar manner, the RADIANCE two-cohort design will potentially allow future development and eventual regulatory approval of Paradise System renal denervation in combination with multiple drug combinations/and or doses.

6.7. ***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.[xlv] Furthermore, precedence from pharmaceutical evaluations of antihypertensive medication[xlvi]and from the recently presented DENERHTN[xxxii], Symplicity Flex[xlvii] and Symplicity Japan[xlviii] 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.

6.8. *Minimization of Risk*

Since RADIANCE-HTN is the first randomized, blinded and controlled trial of the Paradise ultrasound technology, the following specific measures have been taken to ensure that subjects are not inappropriately exposed to an increased risk of cardiovascular events including stroke and/or renal stenosis:

- Drug discontinuation in the RADIANCE Solo cohort will occur in line with accepted Institutional guidelines for a subjects' current medication and subjects whose baseline eligibility systolic/diastolic office BP is ≥180/110 mmHg or baseline daytime ABP is ≥170/105 mmHg are excluded
- Drug discontinuation in the RADIANCE Solo cohort 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]
- All subjects will be provided with home BP monitoring devices from the point of a) drug discontinuation or run-in (RADIANCE Solo cohort) or b) initiation of fixed dose triple combination therapy (RADIANCE Trio cohort)
- Subjects whose average home BP increases to ≥170 systolic or ≥105 mmHg diastolic and who have clinical events considered to be related to persistent or elevated hypertension pre-randomization such that a change in medication is necessitated, will be excluded
- Subjects whose average home BP increases to ≥170 systolic or ≥105 mmHg diastolic at any time post randomization will be eligible to have their antihypertensive medication restarted or modified as needed
- Subjects in the RADIANCE Solo cohort will have antihypertensive drug therapy initiated immediately following the 2 month FU if needed
- Non-invasive imaging will be required for all subjects at baseline (CTA/MRA at a minimum), the 2 and 6 month FUs (duplex ultrasound) and for all treated subjects at the 12 month FU (CTA/MRA) and the 24 and 36 month FUs (duplex ultrasound)

7. Subject Selection

7.1. *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.

**According to National or Institutional guidelines e.g. "Clinical management of primary hypertension in adults", NICE Hypertension Guidelines, August 2011*

7.2. *Inclusion Criteria*

Male and female subjects who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion is met. Minor differences in inclusion criteria exist for the RADIANCE Solo cohort versus the RADIANCE Trio cohort reflecting the different stage in hypertension progression of each group:

7.2.1. Inclusion Criteria - RADIANCE Solo

Subjects who meet any one of the following criteria should be given consideration for inclusion in the Solo Cohort:

- Appropriately signed and dated informed consent
- Age ≥18 and ≤75 years at time of consent
- Documented history of essential hypertension
- Either,
    - average seated office BP <180/110 mmHg at screening visit (V0) while on a stable regimen of 1 or 2 antihypertensive medications for at least 4 weeks prior to consent or,
    - Average seated office BP ≥ 140/90 mmHg <180/110 mmHg despite lifestyle measures on no antihypertensive medications
- Documented daytime ABP ≥135/85 mmHg and <170/105 mmHg 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) renal imaging)
- Able and willing to comply with all study procedures

7.2.2. Exclusion Criteria - RADIANCE Solo Cohort

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

- Renal artery anatomy on either side, ineligible for treatment including:
    - Main renal artery diameter < 4 mm and > 8 mm
    - Main renal artery length < 25 mm
    - A single functioning kidney
    - Presence of abnormal kidney (or secreting adrenal) tumors
    - Renal artery with aneurysm
    - Pre-existing renal stent or history of renal artery angioplasty
    - Prior renal denervation procedure
    - Fibromuscular disease of the renal arteries
    - Presence of renal artery stenosis of any origin ≥ 30%
    - Accessory arteries with diameter ≥2mm <4 mm and > 8 mm*
- Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter
- Evidence of active infection within 7 days of procedure
- Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma Hb1Ac ≥ 9.0%)
- Documented history of chronic active active inflammatory bowel disorders such as Crohn's disease or ulcerative colitis
- eGFR of <40 mL/min/1.73 m2 (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 (myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV)
- Documented confirmed episode(s) of stable or unstable angina
- Documented repeat (>1) hospitalization for hypertensive crisis within the prior 12 months

- 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
- 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
- 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 (e.g. night shift workers)
- Pregnant, nursing or planning to become pregnant (documented negative pregnancy test required documented within a maximum of 7 days prior to procedure for all women of child bearing potential. Documentation of effective contraception is also required for women of child bearing potential)
- Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable)

** This 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*

7.2.3. Inclusion Criteria - RADIANCE Trio Cohort

Subjects who meet any one of the following criteria should be given consideration for inclusion in the Trio Cohort:

- Appropriately signed and dated informed consent
- Age ≥18 and ≤75 years at time of consent
- Documented history of hypertension
- Average seated office BP ≥140/90 mmHg at screening visit (V0) while on a stable regimen of at least 3 antihypertensive medications of different classes including a diuretic for at least 4 weeks prior to consent
- Documented daytime ABP ≥ 135/85 mmHg after 4-week stabilization 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) renal imaging)
- Able and willing to comply with all study procedures

7.2.4. Exclusion Criteria - RADIANCE Trio Cohort

Subjects who meet any one of the following criteria will be excluded from the Trio Cohort.

- 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
- Evidence of active infection within 7 days of procedure
- Secondary hypertension not including sleep apnea (documented through clinical work up within the 12 months prior to consent- see Section 7.2.4.1)
- Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma Hb1Ac ≥ 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) within 3 months prior to consent
- Any history of severe cardiovascular event (myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV) within 3 months prior to consent
- Documented confirmed episode(s) of unstable angina within 3 months prior to consent
- Documented intolerance or contraindication for any of the antihypertensive drugs prescribed as a requirement of the study protocol
- Documented repeat (>1) hospitalization for hypertensive crisis within the prior 3 months
- Prescribed to any standard anti-hypertensive CV medication (other than beta blockers) for other chronic conditions (e.g. ischemic heart disease) such that discontinuation might pose serious risk to health
- 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 (documented negative pregnancy test required documented within a maximum of 7 days prior to procedure for all women of child bearing potential. Documentation of effective contraception is also required for women of child bearing potential)
- Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional Registries is acceptable)

** This 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*

7.2.4.1. Secondary Hypertension

It is important to ensure that in treatment resistant hypertensive subjects, potential secondary causes of hypertension are ruled out. It is expected that evidence of clinical work up to exclude the most commonly diagnosed secondary forms of hypertension will have been documented within the 12 months prior to subject consent. Study-required tests can also be used to diagnose causes of secondary hypertension as needed (e.g. baseline blood and urine chemistry CTA/MRA). Secondary forms of hypertension are shown in Table 7.2-1 (adapted from the Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure[ii] and ESH/ESC 2013), as well as instances in which it would be expected that additional testing would be required in the absence of existing documentation. Subjects with sleep apnea are NOT excluded.

Table 7.2-1: Secondary Hypertension Screening

Condition	Screening test	Comment
Primary Aldosteronism	Plasma aldosterone/renin ratio/24-hour urinary aldosterone. Adrenal CT if needed	Documentation of exclusion in TRIO cohort will be required (acceptable within 1 year of consent) but can be excluded via the study-defined imaging (CTA/MRA) by visualization of the adrenal glands
Renovascular Hypertension	CT angiography; MR Angiography; renal angiogram	Documentation of exclusion in TRIO cohort will be required (acceptable within 1 year of consent) but can be excluded via study-defined imaging (CTA/MRA) and renal angiogram if required
Pheochromocytoma	History/ 24-hour urinary or plasma metanephrine and normetanephrine	Presence of secreting adrenal tumors is already an exclusion criteria for both the SOLO and the TRIO cohort. Can be excluded via study-defined imaging including CTA and MRA if required
Chronic Kidney Disease	Estimated glomerular filtration rate (eGFR); spot urine test for albumin/creatinine ratio,	An eGFR of <40 mL/min/1.73 m^2 is an exclusion criteria for both the SOLO and the TRIO cohort.
Hypothyroidism/ Hyperthyroidism	Thyroid Stimulating Hormone tests (TSH) Thyroxine/Triiodothyronine	Documentation of testing only required in the event of clinical suspicion physical/history etc
Cushing Syndrome	History/physical	Rare. Documentation of testing only required in the event of clinical suspicion physical/history etc
Coarctation of the Aorta	CTA or MRA imaging	Rare. Documentation of testing only required in the event of clinical suspicion based on physical/history etc
Hyperparathyroidism	Hypercalcemia	Rare. Documentation of testing only required in the event of clinical suspicion physical/history etc

8. Subject Accountability

8.1. *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 and full exclusion of secondary hypertension may only be confirmed during the active renal angiogram procedure) enrolled subjects will only count towards the enrollment ceiling at the time of randomization.

8.2. *Re-Consent*

Under specific circumstances, a subject that has previously been found to be ineligible for the study during screening ("Screening Failures – see Section 8.4) 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 etc.). Any subject that is being considered for re-consent will be approved by the Sponsor.

8.3. *Withdrawal*

All subjects included in the RADIANCE study (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; email; letter). 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

Return of home BP monitoring systems after withdrawal for reasons of physician or subject preference is recommended. Withdrawal from the study will be documented on the Study Status form

8.4. *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 should 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 30 days. Home BP devices will be returned to the investigational center.

- Attempt: A subject who signs the informed consent, meets eligibility criteria and has any form of anesthesia/analgesia administered for the procedure but was not successfully treated per the protocol. This includes subjects excluded by renal angiogram. All attempt subjects will be followed for 30 days post procedure for safety and any adverse events that occur within that period will be collected. Follow-up can be conducted by phone, email, office visit. Home BP monitors should be returned to the investigational center for these subjects. Exit from the study will be documented on the Study Status form.
- 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 enrollment ceiling even in the event that the treatment was not completed per protocol. These subjects will be provided with a Home BP Monitor for the duration of the study.

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

9. Methods

9.1. *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 9.1-1 summarizes the study visit schedule (see text for details):

Table 9.1-1: 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	NA	30±7	60±7	90±7	120±7	150±7	180±7	360±14	720±30	1080±30	1440±60	1880±60
Informed consent	X															
Average Office BP*	X	X			X[+]	X	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	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				
HTN Medication Withdrawal (Solo Cohort)	X	X	X	X	X	X	X									
Triple HTN Therapy (Trio Cohort)	X	X	X	X	X	X	X	X	X	X	X∞					
HTN Therapy Escalation (if needed per BP criteria)							X	X	X	X	X	X				
12-lead ECG		X	X≠				X				X	X				
Renal Duplex Ultrasound			X¥			X[$]	X	X[$]	X[$]	X[$]	X	X[$]	X[T]	X[T]		
CTA/MRA			X**				X[$]				X[$]	X[T]				
Urine Chemistry			X				X				X	X				
Urine for Drug Metabolite (Trio Cohort Only)			X				X				X					
Blood Chemistry			X				X				X	X				
Plasma for Biomarkers (Solo Cohort Only - optional)			X				X				X	X				
Pregnancy Test (where applicable)			X#													
Diagnostic renal angiogram				X												
Randomization				X												
Renal Denervation Procedure				X[T]												
Pain Perception Evaluation (Visual Analog Scale)				X	X											
Blinding Index					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 from an average of a minimum of 3 seated measurements as well as standing measure unless specified (See Section 10.1)*
+ Measurement of Standing Office BP is optional at Discharge Visit
∞ Triple HTN therapy is continued up to the 6-month visit. Following completion of the 6-month visit, antihypertensive medication is per physician discretion
≠ If not done at Baseline Visit V1
¥ Recommended. A recent (within 6 months of consent) good quality renal duplex ultrasound is acceptable
 # within a maximum of 7 days prior to procedure
$ if required in the event of clinical suspicion of renal artery stenosis
*** A recent (within 12 months of consent) good quality, renal MRA or CTA is acceptable*
X^T Treated Subjects
€ Home BP readings start 7 days prior to scheduled office visit
Note: Pre-procedure tests may be completed at any time from the point a subject attends the Screening Visit (V0) up to the Procedure. Review of CTA/MRA images by the Sponsor in collaboration with the clinical site is required prior to procedure. Allow sufficient time for scheduling if required.

Table 9.1-2: 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	1880±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				
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				
Renal Duplex Ultrasound					X	X		X	X		
Blood Chemistry	X£				X	X	X				
Urine Chemistry	X£				X	X	X				
Pregnancy Test (where applicable)	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;
**Average seated Office BP will be from an average of a minimum of 3 seated measurements as well as standing measure unless specified (See Section 10.1)*
+ Optional
 # within a maximum of 7 days prior to procedure
£ Results from tests recently performed during study follow-up visits may be used unless there were major changes to the patient condition or treatment.

9.2. *V0: Study Screening Visit*

Subjects who meet general eligibility for consideration for the study will sign an informed consent and be assigned to one of the two study cohorts. All subjects will have their seated average office BP measured (see Section 10.1), a limited medical history review, physical exam and current medication review.

9.2.1. **RADIANCE Solo Cohort**

Subjects eligible for the RADIANCE Solo Cohort currently prescribed to hypertensive BP medication with systolic office BP < 180 mmHg, will be asked to stop taking all hypertensive medication for the 4 week wash-out period (follow Institutional guidelines for wash-out of current hypertension medication). Subjects assigned to the RADIANCE Solo Cohort currently not prescribed to hypertensive BP medication with office BP ≥ 140/90 mmHg < 180/110 mmHg, will be asked to stay medication-free for a 4-week run-in period.

9.2.2. **RADIANCE Trio Cohort**

Subjects eligible for the RADIANCE Trio cohort will be asked to stop their current hypertensive medication and replace it with the study-defined medication regimen (see Section 9.12.2) for the 4-week stabilization period.

All subjects will be provided with a home BP monitoring system, trained on its use and asked to take their home BP (see Section 10.3) for 7 consecutive days prior to the return visit to the investigational site (Baseline Eligibility Visit). They will also be given a patient diary.

Table 9.2-1: Data to be collected during the screening visit (V0)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing BP)	Maintain at site
Limited medical history and physical examination including but not limited to gender, age at consent, height, weight, relevant cardiovascular history	Maintain at site
Renal CTA/MRA Review (if available)	Upload copy
Renal duplex ultrasound review (if available)	Upload copy
Current medication (hypertensive and non-hypertensive)	Maintain at site

9.3. *V1: Baseline Eligibility Visit*

All subjects will return to the clinical center to have their office BP measured 4 weeks (±3 days) after either the discontinuation of their hypertensive medication (or the run-in period for those subjects without prescribed antihypertensive therapy) or the replacement of their current hypertensive medication with the study-defined medication regimen.

It is strongly recommended that the V1 visit occur between 08:00 and 10:00am following an 8-hour overnight fast. RADIANCE Trio subjects will be asked to not take their morning dose of antihypertensive medication but instead to bring their medication with them to the V1 visit. The investigational center may contact the study subject 24-hrs prior to V1 to remind them of the need for overnight fasting and for RADIANCE Trio subjects, to bring their morning hypertensive medication to the FU.

All subjects will have a seated office BP measurement recorded (see Section 10.1) and will undergo ABP measurement following training on how to use the ABP device. Once the device is started, RADIANCE Trio subjects will receive the morning dose of their antihypertensive treatment. Subjects will be requested to return the ABP device within approximately 24 hours. Since this ABP data marks the point of eligibility for the study, it is strongly recommended that subjects return to the clinical center with the ABP device.

Table 9.3-1: Data to be collected during the Baseline Eligibility Visit (V1)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing BP)	Maintain at site
Home BP measurements and review of diary entries	Maintain copy at site
Physical examination	Maintain at site
Current medication (hypertensive and non-hypertensive)	Maintain at site
Documentation of any adverse events	Original at site. Upload copy to database as requested (SAE; SADE)
Protocol Deviations	Maintain at site

9.3.1. Baseline ABP Review and Final Eligibility Testing

Subjects in the RADIANCE Solo cohort whose baseline, daytime ABP is documented to be ≥135/85 mmHg and <170/105 mmHg* and subjects in the RADIANCE Trio cohort whose daytime ABP is documented to be ≥135/85 mmHg, will be considered eligible for the study and asked to complete final pre-procedure eligibility tests (See section 9.3.2).

**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 may be asked to repeat the measurement*

Table 9.3-2: Data to be collected during ABP Review

Data Collection	Location of Source
24-hour ABP report	Upload to core lab. Maintain copy of report at site
Documentation of any adverse events	Original at site. Upload copy to database (SAE; SADE)
Protocol Deviations	Maintain at site

Table 9.3-3: Data to be collected following eligibility by ABP

Data Collection	Location of Source
Review and update of medication history	Maintain at site

Subjects who do not meet the protocol-defined ABP criteria will not be deemed eligible to continue in the study and will be withdrawn from the study and classified as "Screening Failures" (See section8.4). These subjects may then return to standard of care and home BP monitoring systems should be returned to the clinical center.

9.3.2. 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. These tests may be completed pre-emptively

as part of the V1 visit 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 9.3-4: 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
Screening renal duplex ultrasound (optional)	Upload copy
Baseline 12-lead ECG	Maintain at site
Baseline urine (for chemistry both cohort and drug screening – Trio Cohort Only)	Maintain at site
Baseline Blood (for chemistry)	Maintain at site
Baseline Blood (plasma for biomarkers- Solo Cohort Only- optional test)	Maintain 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. For this reason, the CTA/MRA should be scheduled to allow sufficient time for review. In the event the screening CTA or MRA documents an ineligible renal anatomy or evidence for any other exclusion criteria, the subject will not be eligible for the procedure and will be classified as an "Screening Failure" (see section 8.4). These subjects will be withdrawn from the study and may return to standard of care. Home BP systems should be returned to the clinical center. A baseline renal duplex ultrasound is also strongly recommended.

9.4. *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 V1 visit. In the event a procedure cannot be scheduled within that time frame the Sponsor must be notified. Subjects of child bearing potential must have a documented negative pregnancy test dated within a maximum of 7 days prior to the procedure.

9.4.1. Blinding Process

No study personnel who will be responsible for recording patient BP during FU 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. Other methods of blinding such as standardization of length of time spent in the cath lab for blinded controls, removal of clocks in recovery room and prevention of contact between subjects treated on the same day may be considered and will be collected if used.

9.4.2. Hypertensive Medications Pre-Procedure

Any changes in antihypertensive medication since the V1 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.

9.4.3. 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.

9.4.4. 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 7 French guide catheter (minimum diameter; see Section 4.3.2). 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 therefore angiographic evidence of any of the following criteria on either side, would deem the subject as ineligible for randomization:

- Main renal artery diameter < 3 mm > 8mm
- Main renal treatable length < 20mm
    - 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
- Abnormal kidney or secreting adrenal tumor
- Renal artery with aneurysm
- Pre-existing renal stent
- Pre-existing aortic stent
- 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 >8mm

In the event that all these angiographic criteria cannot be confirmed with a global angiogram, a selective renal angiogram may be conducted.

9.4.5. Randomization

Randomization will occur following the diagnostic renal angiogram. Only randomized patients will count towards the enrollment ceiling.

9.4.6. Blinded (Sham) Procedure

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

9.4.7. Renal Denervation Procedure

Specific details of the renal denervation procedure will be provided in the Manual Operations. 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; 7 French). Carefully advance the guide catheter into the left or right renal artery using fluoroscopic guidance. Verify patency by performing an angiogram and measure the distal. mid and proximal artery diameters in order to select the appropriate Paradise catheter balloon size (see Table 9.4-1). Select the Paradise Catheter based on the smallest measured diameter of the artery and follow these steps to deliver treatment bilaterally:

Table 9.4-1: 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 sonicationsIf 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

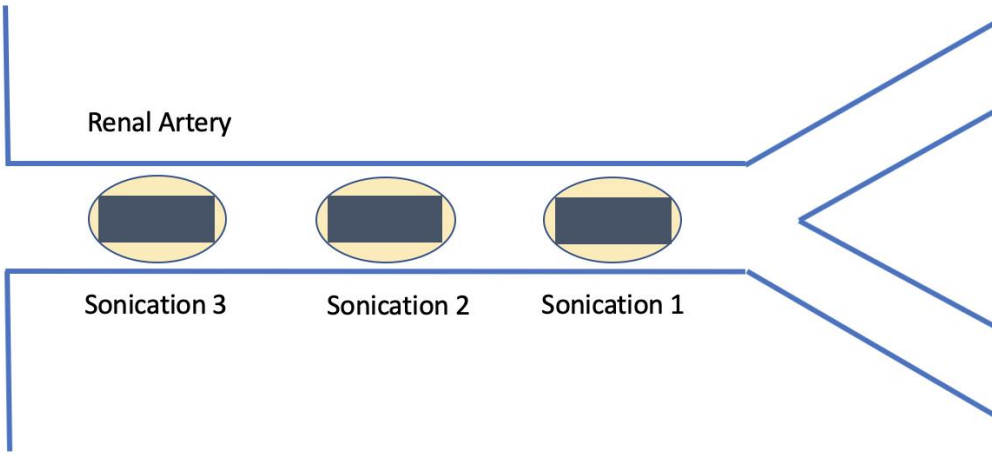
  - If an accessory artery/side branch is present and has a diameter ≥ 3 mm, one (1) sonication should be delivered

- 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

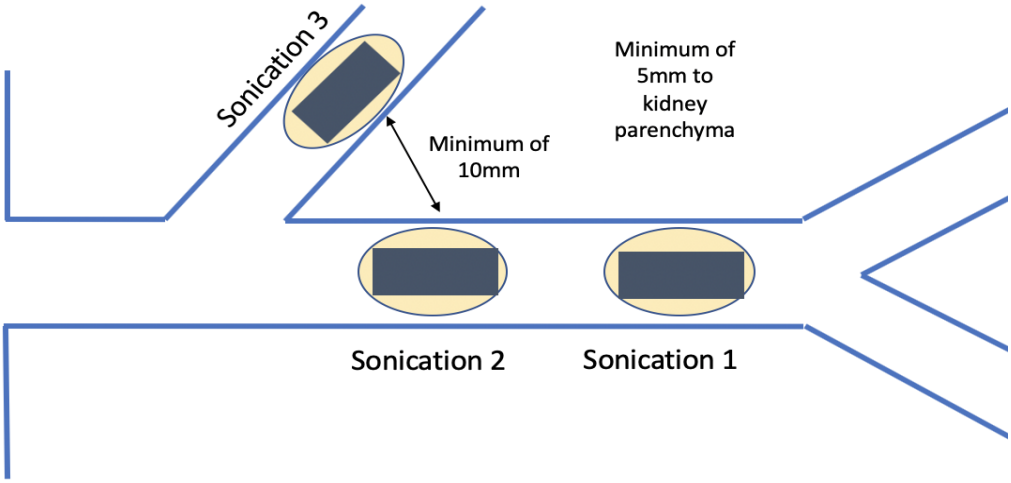
The Paradise catheter and accessories should be returned to the Sponsor. If the devices are not returned, appropriate disposal must be documented.

Figure 9.4-1: Examples of Treatment Strategy in Renal Artery, Accessory Artery, and Proximal Side Branch

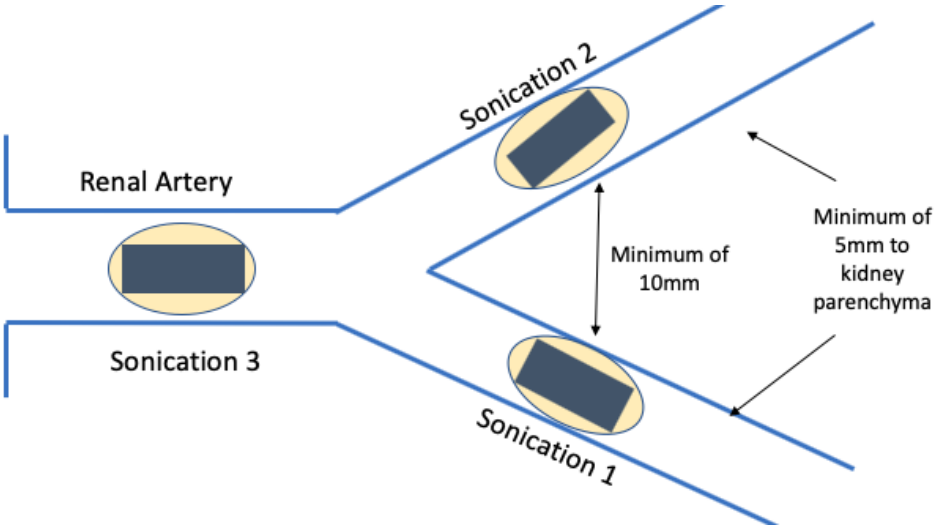
9.4-1a: Three ultrasound sonications in main renal artery



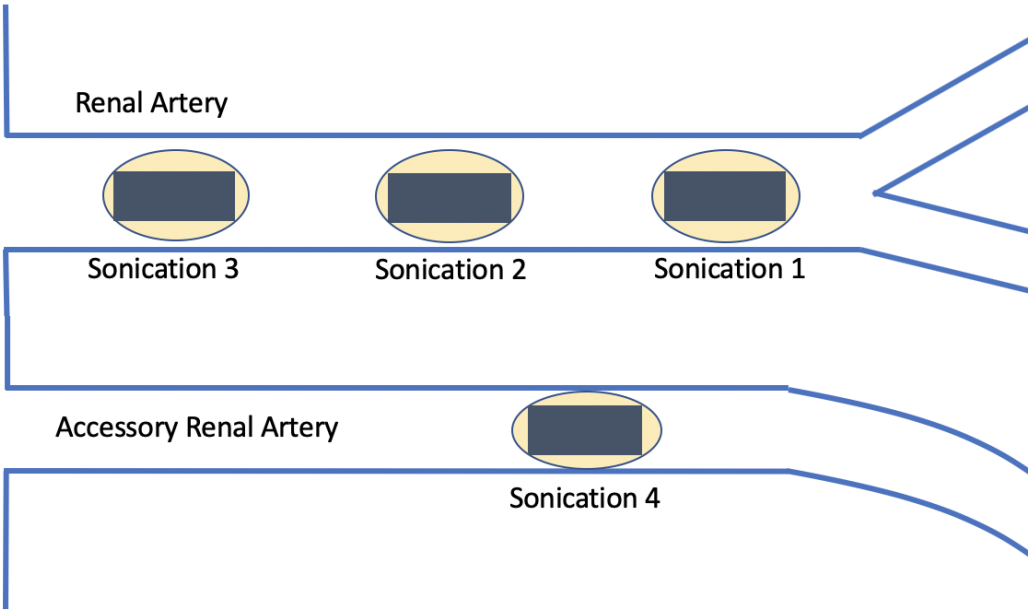
9.4-1b: Two ultrasound sonications in main renal artery and one in proximal side branch artery



9.4-1c: One ultrasound sonication in main renal artery and one in proximal bifurcating branches



9.4-1d: Three ultrasound sonications in main renal artery and one in accessory renal artery



9.4.8. Data Collection

Table 9.4-2 documents the data to be collected during the renal denervation or blinded control (sham) procedure.

Table 9.4-2: Data to be collected during the Procedure (P1)

Data Collection	Location of Source
Visual Analog Pain Assessment (prior to procedure)	Upload copy to database
Procedure times (femoral access to femoral closure)	Maintain at site
Procedural Medication (temporary anti-hypertensive medication; anesthesia; analgesia; anticoagulation if used; contrast volume; radiation dose etc.)	Maintain at site
Renal anatomy detail from renal angiogram (global or selective)	Upload copy. Maintain copy of report at site
Randomization	CRF or equivalent
Procedural angiogram	Upload copy. Maintain copy at site unless requested
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 database (SAE, SADE)
Device Deficiencies	Upload copy to database
Protocol Deviations	Maintain at site

9.4.9. Post Procedural Pain Assessment

Subjects will be asked to complete a Visual Analog Pain Assessment (see Appendix A) prior to the procedure and again before they leave the hospital.

9.5. *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 follow-up. Table 9.5-1 documents the data to be collected prior to discharge from the hospital.

Table 9.5-1: Data to be collected prior to Discharge (D1)

Data Collection	Location of Source
Average office BP Measurement per guidelines (measurement of standing office BP is optional)	Maintain at site
Visual Analog Pain Assessment	Upload copy to database
Blinding Index	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

Following discharge from the hospital, subjects will remain in their assigned cohort at least through the 2-month FU visit, with respect to remaining free of hypertensive medication (RADIANCE Solo Cohort) or compliant with the study-prescribed fixed drug regimen (RADIANCE Trio Cohort) unless in the event of a BP emergency or other clinical events that deem a change of medication may be necessary (see Section 9.12).

9.6. *In Clinic Follow-up Visits*

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. Home BP measurements will be collected for the 7 consecutive days prior to the office visit up to and including the 12-month FU (see Section 10.3). It is recommended that the investigational site contact the subject approximately 7 days prior to the office visit to remind them to begin their Home BP measurements.

It is strongly recommended that all in-clinic visits be scheduled between 08:00 and 10:00am following an 8-hour overnight fast. Subjects taking study-defined antihypertensive medication at any time during the trial will be asked to not take their morning dose of antihypertensive medication but instead to bring their medication with them to the visit. The investigational center may contact the study subject 24-hrs prior to each visit to remind them of the need for overnight fasting and to bring their morning hypertensive medication to the FU (See Section 9.12).

9.6.1. **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 9.6-1 documents the data to be collected.

Table 9.6-1: Testing to be collected at one month visit (V2)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
Home BP measurements and review of diary entries	Maintain copy at site
Physical examination	Maintain at site

Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

9.6.2. 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 6-month FU visit. Changes in hypertension medication are permissible in both cohorts following the two month visit as described in Section 9.12. Table 9.6-2 documents the data to be collected.

Table 9.6-2: Testing to be collected at two month visit (V3)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
24-hour ABP report*	Upload to core lab. Maintain copy of report at site
Home BP measurements and review of diary entries	Maintain copy at site
Urine (for chemistry – both cohort and drug screening – Trio Cohort Only)	Maintain at site
Blood (for chemistry)	Maintain at site
Blood (plasma for biomarkers- Solo Cohort only- Optional test)	Maintain at site
12-lead ECG	Maintain at site
Renal Duplex Ultrasound	Upload copy. Maintain copy of report at site
Physical examination	Maintain at site
Changes in medication	Maintain at site
Blinding Index	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

**Note: in the event insufficient data is available following the 24-hr ABP recording to determine eligibility, the subject will be asked to repeat the measurement*

9.6.3. 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 9.6-3 documents the data to be collected.

Table 9.6-3: Testing to be collected at three month visit (V4)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
Home BP measurements and review of diary entries	Maintain copy at site
Physical examination	Maintain at site

Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

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

Subjects will be required to return to the clinical center four (4) months post procedure during. Table 9.6-4 documents the data to be collected.

Table 9.6-4: 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
Home BP measurements and review of diary entries	Maintain copy at site
Physical examination	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

9.6.5. 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 9.6-5 documents the data to be collected.

Table 9.6-5: Testing to be collected at five month visit (V6)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
Home BP measurements and review of diary entries	Maintain copy at site
Physical examination	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

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

Subjects will be required to return to the clinical center six (6) months post procedure. The six month visit marks the end of the period of blinding for all subjects and hypertensive medication changes can be made per the discretion of the investigator after this visit. The six month FU also marks the minimum point at which Control patients may cross-over to treatment. Investigators will be informed when cross-overs may occur. Table 9.6-6 documents the data to be collected.

Table 9.6-6: Testing to be collected at six month visit (V7)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
24-hour ABP report*	Upload to core lab. Maintain copy of report at site
Home BP measurements and review of diary entries	Maintain copy at site
Blinding Index (record prior to un-blinding subject)	Maintain at site
Urine (for chemistry – for both cohorts and drug screening Trio Cohort Only)	Maintain at site
Blood (for chemistry)	Maintain at site
Blood (plasma for biomarkers- Solo Cohort only- Optional test)	Maintain at site
12-lead ECG	Maintain at site
Renal duplex ultrasound	Upload copy. Maintain copy of report at site
Physical examination	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

**Note: in the event insufficient data is available following the 24-hr ABP recording to determine eligibility, the subject will be offered the opportunity to repeat the measurement*

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

Subjects will be required to return to the clinical center twelve (12) months post procedure. Table 9.6-7 documents the data to be collected.

Table 9.6-7: Testing to be collected at twelve month visit (V8)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
24-hour ABP report*	Upload to core lab. Maintain copy of report at site
Home BP measurements and review of diary entries	Maintain copy at site
Urine (for chemistry)	Maintain at site
Blood (for chemistry)	Maintain at site
12-lead ECG	Maintain at site
Treated Subjects: renal CTA or MRA	Upload copy. Maintain copy of report at site
Physical examination	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

9.6.8. V9, V10, V11 & V12: Twenty-Four (720±30), Thirty-Six (1080±30), Forty-Eight (1440±60) & Sixty (1880±60) Month Visits

Subjects will be required to return to the clinical center twenty-four (24), thirty-six (36), forty-eight (48) and sixty (60) months post procedure. The sixty month visit marks the end of the study-defined period of FU for all subjects who have not elected to cross-over (if applicable, see Section 9.7). Table 9.6-8 documents the data to be collected.

Table 9.6-8: Testing to be collected at 24, 36, 48 & 60 Month visit (V9, V10, V11, V12)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
Treated Subjects: Renal duplex ultrasound (24 & 36 Month Only)	Upload copy. Maintain copy of report at site
Physical examination	Maintain at site
Changes in medication	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

9.7. *Cross-Over to Treatment*

In the event that cross-over to treatment is authorized, clinical sites will be informed by the Sponsor. Subjects that elect to cross-over will be followed according to the following schedule:

- Cross-over Baseline Evaluation (COV1)
- Cross-over Procedure (COP2)
- Cross-over Discharge (COD2)
- Cross-over 1-month FU (COV2)
- 2- month FU (COV3)
- Cross-over 6 month FU (COV4)
- Cross-over 12 month FU (COV5)
- Cross-over 24 month FU (COV6)
- Cross-over 36 month FU (COV7)
- Cross-over 48 month FU (COV8)
- Cross-over 60 month FU (COV9)

9.7.1. Cross-Over Data Collection

The cross-over procedure should be conducted according to the detail in Section 9.4.6. The data to be collected during Cross-Over baseline is shown in Table 9.7-1

Table 9.7-1: Data to be collected at Cross-over Baseline FU (COV1)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
Cross-over eligibility evaluation	Maintain at site

24-hr ABP report*£	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
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 database (SAE, SADE)
Protocol Deviations	Maintain at site

**Note: in the event insufficient data is available following the 24-hr ABP recording to determine eligibility, the subject will 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.

The data to be collected during Cross-Over procedure is shown in Table 9.7-2.

Table 9.7-2: Data to be collected during the Cross-Over Procedure (COP2)

Data Collection	Location of Source
Procedure times (femoral access to femoral closure)	Maintain at site
Procedural Medication (temporary anti-hypertensive medication; anesthesia; analgesia; anticoagulation if used; contrast volume etc.)	Maintain at site
Renal anatomy detail from renal angiogram (global or selective)	Upload copy. Maintain copy of report at site
Procedural angiogram	Upload copy. Maintain copy 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 database (SAE, SADE)
Device Deficiencies	Upload copy to database
Protocol Deviations	Maintain at site

Hospital discharge should be conducted according to the detail in Section 9.5 other than the need for Pain Assessment and Blinding Index. Table 9.7-3 documents the data to be collected prior to discharge from the hospital for cross-over subjects

Table 9.7-3: Data to be collected prior to Cross-over Discharge (COD2)

Data Collection	Location of Source
Average office BP Measurement per guidelines (measurement of standing office BP is optional)	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

Subjects will be required to return to the clinical center one (1) month post cross-over procedure. Table 9.7-4 documents the data to be collected for cross-over subjects.

Table 9.7-4: Data to be collected at Cross-over 1 month FU (COV2) post cross-over procedure

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Limited physical examination	Maintain at site
Changes in medication	Maintain at site
Protocol Deviations	Maintain at site

Ambulatory and office BP measurements should be recorded at the 2, 6 and 12 month FUs for all cross-over subjects. A CTA/MRA should be recorded in all cross-over subjects at the 12 month FU. Table 9.7-5 documents the data to be collected at FU.

Table 9.7-5: Data to be collected at 2, 6 & 12 month cross-over FUs (COV3, COV4, COV5)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
24-hour ABP report*	Maintain copy of report at site
Renal duplex ultrasound (2 & 6 month FU)	Upload copy. Maintain copy of report at site
Renal CTA or MRA (COV5- 12 Month FU Only)	Upload copy. Maintain copy of report at site
Limited physical examination	Maintain at site
Changes in medication	Maintain at site
Blood (for chemistry)	Maintain at site
Urine (for chemistry)	Maintain at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
Protocol Deviations	Maintain at site

**Note: in the event insufficient data is available following the 24-hr ABP recording to determine eligibility, the subject will be asked to repeat the measurement.*

Table 9.7-6 documents the data to be collected at FUs.

Table 9.7-6: Data to be collected 24- month, 36-month, 48-month & 60-month cross-over FU (COV6, COV7, COV8 & COV9)

Data Collection	Location of Source
Average office BP Measurement per guidelines (including standing office BP)	Maintain at site
Limited physical examination	Maintain at site
Changes in medication	Maintain at site
Renal duplex ultrasound (24 month & 36 month only)	Upload copy. Maintain copy of report at site
Adverse Events	Original at site. Upload copy to database (SAE, SADE)
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.

9.8. *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.

As part of the Unscheduled Follow-up, if any of the following assessments/procedures are performed, they should be reported in the database: Medical History; Physical Examination; Medications; Office Blood Pressure; Home Blood Pressure; Ambulatory Blood Pressure; 12-lead ECG; Renal Duplex Ultrasound; Non-invasive imaging (CTA/MRA); Urine Chemistry; Blood Chemistry; Plasma for Biomarkers; Pregnancy Test.

9.9. *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).

9.10. *Extended Follow-up Period*

All subjects will be followed for five (5) years post procedure. Subjects would be followed per standard of care for their Institution with continued adverse event collection and reporting. The information collected during these regular follow-up visits will be reported via the electronic data capture (EDC) system, as outlined in Tables 9.1-1, 9.1-2. 9.6-8 & 9.7-6. DSMB review of clinical event information will continue to occur as specified in the DSMB charter.

9.11. *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.

9.12. *Study Medication*

Throughout the study, subjects will be instructed about the importance of medication adherence and asked to take any required study-defined antihypertensive 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. This applies to subjects in the Trio cohort as well as any subjects that begin antihypertensive medication at any time during the study.

At all times the safety and well-being of the subject are of primary concern. For the period of wash-out/run-in (RADIANCE Solo) or stabilization (RADIANCE Trio) 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 antihypertensive drug wash-out 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 that means a change in medication becomes necessary.

Following the 2 month Primary Efficacy endpoint visit, all subjects will remain blinded up to the 6 month visit. After the 6 month FU visit subjects will be un-blinded and are eligible to be treated per physician discretion

Between the 2 and 6 month FU visits, pre-defined escalation of antihypertensive medication is strongly recommended in both cohorts. The medication escalation will start at the FU where a sustained elevation (≥135 mmHg systolic OR ≥ 85mmHg diastolic) in 7-day home BP measurement is documented (confirmed by office BP ≥ 140 or ≥ 90 mmHg if required per Institutional practice). Drugs will be added sequentially at each monthly FU in the event BP remains elevated. In the event BP remains <135/85 mmHg, no action is required. More frequent introduction of medication is permissible at the discretion of the Investigator in the event that BP remains ≥135 mmHg systolic or ≥ 85 mmHg diastolic.

9.12.1. **RADIANCE Solo Cohort Study Medication**

Since the RADIANCE Solo cohort by definition remains free of antihypertensive medication through to the 2-month Primary Efficacy endpoint visit unless necessitated as described above and in Section 9.13, introduction of antihypertensive therapy may occur as needed following the measurement of the 2 month ABP. Introduction of antihypertensive medication should occur sequentially in the order indicated below in Table 9.12-1 unless otherwise medically indicated.

Table 9.12-1: Solo Cohort Drug Escalation

RADIANCE Solo Cohort		
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		

9.12.2. **RADIANCE Trio Cohort Study Medication**

All subjects assigned to the RADIANCE Triple Cohort will have their current hypertensive medication regimen replaced* for a minimum of approximately 3 months starting with a 4-week stabilization period prescribed, to a single pill, fixed dose, triple combination, anti-hypertensive medication of Amlodipine (10 mg); Valsartan (160 mg) or Olmesartan (40 mg) and Hydrochlorothiazide (25 mg). In the event of leg edema the Amlodipine dose can be reduced to 5 mg. This combination will be taken through to the two month Primary Efficacy endpoint FU visit. During this period, changes in antihypertensive medication may not occur

unless as described above and in Section 9.13. Introduction of additional antihypertensive therapy may occur as needed following the measurement of the 2 month ABP. Introduction of antihypertensive medication should occur sequentially in the order indicated below in Table 9.12-2 unless otherwise medically indicated.

**Note: Subjects with uncontrolled, treatment resistant hypertension currently prescribed to Tribenzor/Sevikar HCT or Exforge HCT (including generics) are eligible. Subjects will be followed for a 4 week stabilization period prior to confirming ABP according to the requirements of the protocol*

Table 9.12-2: Trio Cohort Drug Escalation

RADIANCE Trio Cohort		
Escalation Step	**Drug Class**	**Recommended drugs**
0	None	NA
1	Aldosterone antagonist	Spironolactone: 25 mg
2	Long acting, cardioselective Beta-1 receptor blocker: full dose	Bisoprolol: 10 mg
3	Central Alpha-2 receptor agonist: full dose	Clonidine: 0.1-0.2 mg; Rilmenidine: 1-2mg; Moxonidine 0.2-0.4 mg
4	Long acting Alpha-1 receptor blocker: full dose	Slow release Prazosin 5-10 mg; Doxazosin 4-8 mg
Note: All recommended doses are once daily other than for Clonidine, Rilmenidine or Moxonidine which should be added twice daily at their higher doses		

9.13. *Medication Changes due to BP Emergency*

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

Since the aim of the RADIANCE-HTN study is to determine the effectiveness of renal denervation without medication changes confounding the results, it is intended that baseline hypertensive medication (or lack of it), be maintained through the Primary Efficacy endpoint visit which occurs two months after randomization. However in cases where medication changes are considered medically necessary (e.g. a significant change in BP or adverse events directly related to BP variations or BP medications), medication and/or doses may be adjusted according to the following guidelines:

9.13.1. **Low BP Action**

The dosage of study-defined drugs can be reduced temporarily or discontinued permanently for any subjects whose office systolic BP is reduced to <110mmHg with associated signs and symptoms of hypotension or reduced renal perfusion or an increase in plasma creatinine ≥ 30%. The order in which antihypertensive drugs should be discontinued will depend upon the subjects' assigned cohort (Solo or Trio) and the stage that they are within the scheduled FU. When medically appropriate, for all subjects in whom hypertension medication escalation has started since the 2 month FU visit, down-titration or discontinuation of hypertensive medication is recommended to 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.). For subjects in the RADIANCE Trio cohort prescribed only to the single pill, fixed dose combination, reducing or stopping the current dose of HCTZ should be a first step with subjects then being switched to a double combination CCB + ARB (Sevikar® or Exforge®). All changes in antihypertensive treatment will be documented and patient BP data will be included as per intention-to-treat.

9.13.2. **High BP Action**

Clinical intervention may be required for patients who have clinical adverse events felt to be related to persistent or elevated hypertension at any visit after randomization defined by average 7 day home BP ≥170 (systolic) or ≥105 mmHg (diastolic) and subsequently confirmed by office BP ≥180 or ≥120mmHg (if confirmation is required per Institutional practice). In these circumstances and assuming the subject is post-randomization, the treatment regimen should follow the hypertension medication escalation algorithm as described in Section 9.12.1 and 9.12.2.

In the event that a hypertensive emergency as defined above (i.e with associated clinical events felt to be related to persistent or elevated hypertension) is documented prior to randomization, the subject will be treated per Institutional guidelines and withdrawn from the study.

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

10. Study Defined Procedures/Testing

10.1. *Office Blood Pressure Measurements*

All clinical sites will be provided with an office BP system (either the Omron® MIT ELITE Plus or M10-IT, Omron Co., Kyoto, Japan-). In the event either of these devices becomes unavailable during the course of the study, a commercially equivalent model may be substituted). The same model must be used for any given subject throughout the course of the study. It is also recommended that the office BP system used to collect the V0 screening measurements be provided to the subject for the home BP measurements should they move forward (see Section 10.3). Measurement of office BP will occur at all clinic visits and at discharge and must 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 2013 ESH/ESC Guidelines for the management of arterial hypertension and the JNC-7 2003 Report on prevention, detection, evaluation and treatment of high BP:

- Healthcare providers must ensure that devices for measuring BP are regularly inspected, properly validated, maintained and regularly recalibrated according to manufacturers' instructions
- The operator should be trained and regularly retrained in the standardized technique
- Standardize the subjects' environment and provide a relaxed, temperate setting, with the person quiet and seated, their feet on the floor and their arm outstretched at heart level and supported
- Caffeine, exercise and smoking should be avoided for at least 30 minutes prior to the measurement
- Allow the subjects to sit quietly in a chair for at least 5 minutes before beginning
- If using an oscillometric semi-automated BP monitoring device, ensure that the device is validated and an appropriate cuff size for the person's arm is used. The size of the bladder within the BP cuff must encircle at least 80% of the arm
- Determine the arm which will be used for all blood pressure measurements. Women who have undergone a mastectomy should have blood pressure measured from the

opposite side to the mastectomy. For all others, take an initial BP measurement in both arms. Document and use the arm with the higher systolic reading. Ensure that the same arm is used at each FU. If the difference in readings is > 15 mmHg, repeat the measurements. If the difference in readings between arms remains > 15 mmHg on the second measurement, measure subsequent blood pressures in the arm with the higher reading

- For study defined BP measurements. Take three BP measurements, spaced 1–2 min apart, with the adapted cuff placed at the level of the brachial artery. You may add additional measurements if the three are quite different (>15 mmHg difference between highest and lowest). Document the average BP from the second and third measurements. In the event that more than three measurements are made, use the final two for the average BP calculation
- BP will also be measured 1 min after resuming the standing position. Office heart rate will be determined using the same device

10.2. *24-hour ABP Measurements*

The measurement of 24-hr ABP will occur at baseline, 2, 6 and 12 month FU visits.

- Train subjects on the use of the ABP system (Microlife® WatchBP 03; Microlife, Taipei, Taiwan) and ask them to return approximately 24-hrs later with the ABP Monitor to download the ABP data (transport of ABP systems to the clinical center may be arranged at the discretion of the Investigator).
- The ABP system will be provided by the clinical center to the subject 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 Manual of Operations
- 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
- BP will be measured every 20 minutes during daytime (07:00-22:00 hours) and every 30 min overnight (22:00-07:00 hours).
- Only ABP recordings with a minimum of 21 measurements during the daytime period will be considered valid[xlix]. 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 a repeat ABPM will occur more than 2 days after the original recording, the Sponsor must be notified for agreement.

10.3. *Home BP Measurements*

After education on the use of the Home BP system, all subjects will be provided with a Home BP monitor (Omron® M10-IT, Omron Co., Kyoto, Japan) during the visit at which they are assigned to either cohort. In the event that this device becomes unavailable during the course of the study, a commercially equivalent model may be substituted for new subjects. Subjects will measure their BP at home during the 7 consecutive days prior to each scheduled office FU visit. It is recommended that the clinical site contact the subject to remind them when to begin their 7day Home BP monitoring. 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 as defined in Sections 8.2 and 8.3. The following guidelines for measuring home BP should be followed:

- Measurements will be taken in a quiet room with the subject in a seated position, back and arm supported after at least 5 minutes of rest with the adapted cuff placed at the level of the brachial artery
- Two BP measurements will be made after a period of at least 5 minutes rest, 1-2 minutes apart twice daily. The two measurements should be made once in the morning prior to eating and antihypertensive drug intake (if relevant) and in once the evening after eating. The time that BP measurements are made will be immediately documented in the patient diary
- Ensure that the same arm is used for all Home BP measurements.
- Home BP values will be calculated as the mean of all measurements taken after the first day which will be discarded. A minimum of 18 BP measurements are required for a valid reading

To verify the patient diary entries, it is strongly recommended that the subject bring their home blood pressure device with them to every follow-up and that a report is collected directly from the device. In the event of discrepancies between the diary and the stored report, the report should be considered primary source.

10.4. *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.

10.5. *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 a CTA or MRA needs to be performed specifically for entry into the study, it should occur once ABP eligibility has been confirmed. 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/MRA will be performed 12 months after renal denervation. To ensure consistency around image collection, guidelines for completion of CTA/MRA imaging will be provided by the Sponsor (CLN 0019).

10.6. *Non-Invasive Imaging (Renal Duplex Ultrasound)*

Non-invasive evaluation of the kidneys and renal anatomy during the progression of the study will be done on all subjects (in order to maintain blinding) at the 2 and 6 month FUs and in all treated subjects at the 24 and 36 month FUs, using renal duplex ultrasound. To allow for a direct comparator with images collected at follow-up, a baseline renal duplex ultrasound in addition to the requisite CTA/MRA is strongly recommended. In any event, at any time throughout the duration of the study, if there is any clinical indication or suspicion of any renal anatomical

abnormalities (such as high blood pressure that is extremely hard to control; worsening of previously well controlled blood pressure; elevated blood pressure that affects other organs in the body), diagnosis should be confirmed by a more sensitive imaging method such as CTA/MRA or angiogram. To ensure consistency around image collection, guidelines for completion of non-invasive imaging will be provided by the Sponsor.

10.7. *Laboratory Assessments*

All subjects will have 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 or plasma creatinine (for use in the estimation of glomerular filtration rate- see Section 10.4). 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) and Trio Cohort subjects will have subsequent analysis of antihypertensive compliance. Females of child bearing potential will have a urine or blood plasma pregnancy test up to 7 days prior to the procedure.

10.8. *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.[l] Urine collected for Trio subjects at Baseline, 2 and 6 month FUs will be sent for analysis. Details of the analysis will be documented in the Manual of Operations.

10.9. *Plasma Biomarkers- Optional Assessment*

There is emerging evidence that plasma biomarkers may help identify responders to renal denervation[li,lii] Blood plasma may be collected at Baseline, 2, 6 and 12 month FUs and stored at a minimum of -20ºC for subsequent analysis of the following biomarkers.

- Plasma Immunoreactive Renin
- Aldosterone
- Brain Naturetic Peptide (BNP)
- NT-proBNP
- Copeptin
- Glucose
- Insulin
- HbA1C
- Endothelin-1

11. Data Collection and Statistical Analysis

11.1. *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. Data processing will be

performed in compliance with the EU General Data Protection Regulation (GDPR) 2016/679, and all applicable national laws.

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.

Each data field completed via an EDC system (either 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 (recommended to only be for collection of data points that have no other verifiable source)

11.2. *Statistical Analysis*

Any details of statistical analysis not included in the protocol, can be found in the Statistical Analysis Plan. The primary analysis will be based on the intent to treat population, with subjects analyzed according to their original randomization assignment.

11.3. *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:

$$\text{Ho: } \beta_{txt} = 0$$
$$\text{Ha: } \beta_{txt} \neq 0$$

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. Additional details regarding the Primary Efficacy endpoint will be provided in the Statistical Analysis Plan.

11.4. *Secondary Efficacy Endpoint*

The statistical analysis of the secondary efficacy endpoints will follow the methodology of the primary Efficacy Endpoint but will be based on daytime diastolic ABP; 24-hr ambulatory systolic and diastolic BP; night-time ambulatory systolic and diastolic BP.

11.5. *Safety Assessments*

The assessment of safety will be based primarily on the frequency of serious adverse device effects (SADEs) serious adverse events (SAEs), adverse device effects (ADEs), adverse events (AEs) and laboratory abnormalities classified by Investigators as related to the renal denervation and confirmed by the DSMB. Occurrence and frequency of SADEs and ADEs and AE(s) and SAE(s) will be summarized by treatment group at baseline, last visit and by changes from baseline to last visit for laboratory values. Other safety data will be summarized as appropriate.

11.6. *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

11.7. *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 blinded 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. Randomization in the Trio Cohort will also be stratified by beta blocker usage.

11.8. *Limits on Subjects Enrollment*

Enrollment at any single clinical center will be limited to 20% of the maximum enrollment per cohort in order to prevent a single center from unduly influencing the study results. In addition, approximately 50% of subjects may be enrolled 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.

11.9. *Planned Interim Analyses*

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

11.10. *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 Statistical Analysis Plan. Additional exploratory subgroup analyses may be performed.

11.11. *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.

11.12. *Core Laboratories*

Core laboratories or independent experts will be used to assess and centralize non-invasive imaging, ABP, urine (for drug adherence measurements) and plasma (for the optional biomarker measurements). Specific details related to the core laboratories will be provided in separate Manuals of Operations.

11.12.1. Non-invasive Imaging Core Lab

A core laboratory/independent expert may be used to evaluate any non-invasive imaging collected by CTA /MRA or duplex ultrasound at any time throughout the study. Independent experts will review all follow up CTA/MRA triggered by the renal duplex ultrasound imaging, and for all CTA/MRA collected at 12 months on subjects randomized to treatment, The core lab will not be used to initially determine eligibility per the requirements of appropriate renal anatomy but may be used to:

- Verify subject renal anatomy including the incidence, percentage and progression of renal artery stenosis and other renal artery anatomy abnormalities. 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.

11.12.2. 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

11.12.3. Urine and Plasma Core Lab (CIC1418)

Details of the core lab that will be used to evaluate antihypertensive drug adherence and plasma biomarker analysis are provided below:

CIC1418
Hôpital Européen Georges Pompidou,
Laboratoire du Centre d'Investigation Clinique, 5ème étage pôle D
20-40 Rue Leblanc, 75015 PARIS, France
Phone : +33 (0) 1 56 09 26 55

12. Safety Reporting

12.1. *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 13. AE classification will be according to the following definitions as provided in Table 12.1-1.

Table 12.1-1: 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) *Ref: ISO 14155-2011*	Adverse event related to the use of an investigational medical device 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:

Table 12.1-1: Adverse Event Definitions

Term	Definition
	○ a life-threatening illness or injury, or ○ a permanent impairment of a body structure or a body function, or ○ in-patient or prolonged hospitalization of existing hospitalization, or ○ 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.

Death should not be documented as an AE, but should only be reflected as an outcome of a specific SAE (see Table 12.1-1 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).

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

The Investigator will assess the relationship of any AE to the study device or study procedure as related or unrelated. 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. AEs 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 AEs related to the procedure but not specific to renal denervation (e.g. anesthesia-induced nausea; allergy to contrast etc.). Criteria for determining whether an AE is related or unrelated to the study device are shown in Table 12.2-1:

Table 12.2-1: Criteria for Assessing Relationship of Study Device to AE

Classification	Description
Unrelated	The AE is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The AE is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.
Unknown	• There is no clear evidence to support that the AE is related to the device

12.3. *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 12.3-1.

Table 12.3-1: 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.

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.

12.4. *Investigator Reporting Responsibilities*

The timelines for reporting AEs and device deficiencies to ReCor Medical are shown in Table 12.4-1.

Table 12.4-1: 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	• Within 1 business day of first learning of the event

Table 12.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
	system, an email to ReCor medical with all available information is recommended	
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 Effect	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

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

12.5.1. **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, 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

12.5.2. **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.

13. Potential Risks and Benefits

13.1. *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
- Complications related to anesthesia/monitored anesthesia/conscious sedation
- Death
- Deep vein thrombosis
- Diarrhea
- Dizziness/Syncope/Weakness
- Edema
- Embolism (air, plaque, thrombus, device or other)
- Headache
- Hematoma
- Hematuria
- Hemorrhage
- Hyperhydrosis
- 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

13.2. *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
    - Severe allergy to contrast agent
    - Infection
    - Allergic reaction
    - Hypotension
    - Mild disturbances of heart rate or cardiac conduction
    - Proteinuria, hematuria, electrolyte disturbances
    - Fever
- 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
- 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

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

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

- 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 prescription of single pill, triple combination therapy composed of Amlodipine, Valsartan or Olmesartan and HCTZ (refer to manufacturers brochures for details)
- 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

13.4. *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 in the RADIANCE Solo cohort will occur in line with accepted guidelines for a subjects' current medication and subjects whose baseline eligibility systolic/diastolic office BP is ≥180/110 mmHg or baseline daytime ABP is ≥170/105 mmHg are excluded.
- Drug discontinuation in the RADIANCE Solo cohort is limited to a short period of approximately 3 months during which timeframe subjects are a low risk of any CV event off treatment
- All subjects will be provided with home BP monitoring devices from the point of a) drug discontinuation or run-in (RADIANCE Solo cohort) or b) initiation of fixed dose triple combination therapy (RADIANCE Trio Cohort).
- Subjects whose average home BP increases to ≥170 systolic or ≥105 mmHg diastolic and who have clinical events considered to be related to persistent or elevated hypertension pre-randomization such that a change in medication is necessitated, will be excluded
- Subjects whose average home BP increases to ≥170 systolic or ≥105 mmHg diastolic at any time post randomization will be eligible to have their anti-hypertensive medication restarted or modified as needed
- Subjects in the RADIANCE Solo cohort will have anti-hypertensive drug therapy initiated immediately following the 2 month FU if needed

- Non-invasive imaging will be required for all subjects at baseline (CTA/MRA at a minimum) and at the 2 and 6 month FUs (duplex ultrasound) and for all treated subjects at the 12 month FU (CTA/MRA) and the 24 and 36 month FUs (duplex ultrasound)

13.5. *Anticipated Benefits*

Subjects included in the RADIANCE-HTN Study 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.

13.6. *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.

14. 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 will be documented (via EDC system and/or on CRF) and will be classified according to the categories below in Table 13.6-1:

Table 13.6-1: 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 24hrs
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	Comments; Deviations that do not meet any of the definitions listed above, including those for which the Sponsor provided a waiver.	NA

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.

15. 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.

16. Device/Equipment Accountability

Per 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 (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

17. Compliance

17.1. *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.

17.2. *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, 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

17.3. *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.

17.4. *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).

17.5. *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.

18. 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.

18.1. *Study Monitor*

Study Monitors assigned to the RADIANCE-HTN 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)

18.1.1. **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.

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.

19. 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.

19.1. *Process of Obtaining Informed Consent*

Per 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 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.

20. Committees/Boards

20.1. *Adverse Event Review*

AEs will be collected and reviewed on a continuous basis. Adjudication of AEs will occur in 3 stages:

- Stage 1: Investigator review and initial adjudication at point of data entry
- Stage 2. Sponsor review. Sponsor may query Investigator adjudication in the event there are discrepancies with source.
- Stage 3: All events deemed to be potentially device and/or procedure related and/or potentially serious will be reviewed by an independent physician adjudicator.
- Stage 4. DSMB review and adjudication. The DSMB will provide final, independent review of aggregate events i

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

In addition, events related to any safety criteria pre-specified in the study protocol, plus all unanticipated events, device- or procedure-related events and deaths, will be provided to the DSMB for subsequent review.

20.2. *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 will be responsible for the oversight, review of all relevant AEs including but not limited to:

- All unanticipated events
- All AEs pre-specified as part of the overall safety assessment (see Section 5.2.4)
- All device- or procedure-related events (ADEs and SADEs)
- Deaths

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 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.

20.3. *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.

21. Suspension or Termination

21.1. *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

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

Any investigator, or IRB/ EC involved in the RADIANCE-HTN 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.

21.2.1. **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.

21.2.2. **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.

22. 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 Study 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.

23. 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.

24. 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 HTN 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 [liii], 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[liv]. 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).

25. Abbreviations and Definitions

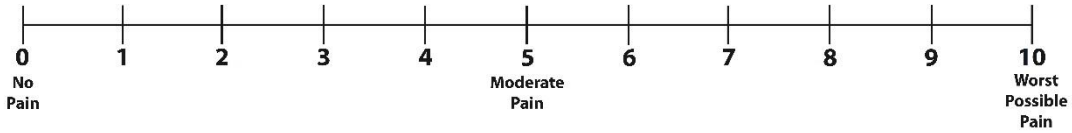
25.1. *Abbreviations*

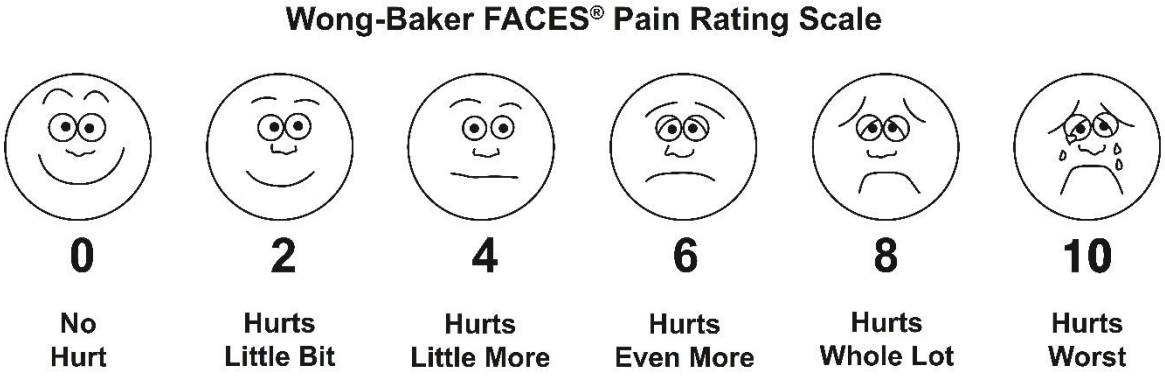
Abbreviations are shown in Table 25.1-1.

Table 25.1-1: Abbreviations

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

26. Appendix A: Visual Analog Pain Scale





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