Medtronic **Clinical Investigation Plan**	
Title	Global Clinical Study of Renal Denervation in the distal main and first order branch renal arteries using the Symplicity Spyral™ multi-electrode renal denervation system (SPYRAL DYSTAL)
Product Name	The Symplicity Spyral™ multi-electrode renal denervation catheter (Symplicity Spyral™ catheter) and the Symplicity G3™ renal denervation RF generator (Symplicity G3™ generator)
Sponsor/ Funding Source	Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, CA United States Regional sponsor: Medtronic Bakken Research Center (BRC) B.V. Endepolsdomein 5 6229 GW Maastricht, The Netherlands
Document version	5.0 – 14 Mar 2022
NCT #	NCT04311086
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1. Glossary

Term	Definition
1M, 3M, 4M, 6M, 12M	1-month, etc. used with follow-up visit windows
2 wk, 6 wk, 8 wk, 10 wk	2-week, etc. used with follow-up visit windows
ABPM	ambulatory blood pressure monitoring
ADE	adverse device effect
AE	adverse event
AH	antihypertensive
BP	blood pressure
CEC	clinical events committee
CIN	contrast-induced nephropathy
CIP	clinical investigation plan
CKD	chronic kidney disease
CRF	case report form
CTA	clinical trial agreement
DC	discharge
DD	device deficiency
DUS	duplex ultrasound
eGFR	estimated glomerular filtration rate
EC	ethics committee
EDC	electronic data capture
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FMD	fibromuscular dysplasia
GCP	good clinical practice
IC	informed consent
IFU	instructions for use
IRB	institutional review board
ITT	intention-to-treat

Term	Definition
MRA	magnetic resonance angiography
OBP	office blood pressure
RDC	remote data capture
RDN	renal denervation
RF	radiofrequency
RX	rapid exchange
SADE	serious adverse device effect
SAE	serious adverse event
SBP	systolic blood pressure
SIV	site initiation visit
SNS	sympathetic nervous system
SV1, SV2	Screening Visit 1, Screening Visit 2
UADE	unanticipated adverse device effect

2. Synopsis

Title	Global Clinical Study of Renal Denervation in the distal main and first order branch renal arteries using the Symplicity Spyral™ multi-electrode renal denervation system (SPYRAL DYSTAL)
Clinical Study Type	Multi-center, international, prospective, interventional, single arm study
Product Name	The Symplicity Spyral™ multi-electrode renal denervation catheter (Symplicity Spyral™ catheter) and the Symplicity G3™ renal denervation RF generator (Symplicity G3™ generator)
EUDAMED number	CIV-19-12-031165
Sponsor	Global sponsor: Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, CA United States Regional sponsor: Medtronic Bakken Research Center (BRC) B.V. Endepolsdomein 5 6229 GW Maastricht, The Netherlands Note: this clinical study is funded by the Global sponsor.
Objective	The objective of this single arm interventional study is to determine if renal denervation performed in the distal main and first order branch renal arteries is as effective in reducing blood pressure as the procedural approach used in the SPYRAL HTN-OFF MED clinical study.
Product Status	Investigational in the United States. Commercially approved in countries that accept CE-mark. (Device will be used in accordance with the *Instructions for Use*.)
Endpoints	**Efficacy endpoints** The efficacy endpoints will be compared to the SPYRAL HTN-OFF MED efficacy endpoints using a propensity score stratified analysis at 3 months. At 6 months and 12 months, the endpoints will be analyzed within the SPYRAL DYSTAL study only. • Change in systolic blood pressure (SBP) from baseline (Screening Visit 2) to 3, 6 and 12 months post-procedure as measured by 24-hour ambulatory blood pressure monitoring (ABPM).

	• Change in office SBP from baseline (Screening Visit 2) to 3, 6, and 12 months post-procedure. • Change in diastolic blood pressure (DBP) from baseline (Screening Visit 2) to 3, 6, and 12 months post-procedure as measured by 24-hour ABPM. • Change in office DBP from baseline (Screening Visit 2) to 3, 6, and 12 months post-procedure. • Incidence of achieving target office SBP (SBP<140 mmHg) at 3, 6, and 12 months post-procedure. • Comparison of the pattern of BP reduction over 24 hours of ABPM between this study and the SPYRAL HTN-OFF MED study. **Safety endpoints** • Safety composite at 1, 3, 6 and 12-months post-procedure: Incidence of the following events: - All-cause mortality - End-stage renal disease (ESRD) - Significant embolic event resulting in end-organ damage - Renal artery perforation requiring intervention - Renal artery dissection requiring intervention - Vascular complications - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol - New renal artery stenosis >70%, confirmed by angiography and as determined by the angiographic core lab at 6 months follow up • Myocardial infarction • Stroke • Renal artery re-intervention • Major bleeding according to TIMI definition (i.e., intracranial hemorrhage, ≥5 g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within seven days of the procedure) • Increase in serum creatinine >50% from Screening Visit 2 The following additional analyses will be conducted: • Procedural characteristics
Study Design	Multi-center, international, prospective, interventional, single arm study treating approximately 50 subjects who will undergo the renal denervation procedure.

Study Population	Subjects with uncontrolled hypertension will be enrolled in accordance with the inclusion and exclusion criteria specified in the protocol. Approximately 350 subjects will be enrolled in order to treat approximately 50 subjects at up to 15 study centers.
Study Duration	Total study duration will be approximately 2.5 years, including enrollment up to minimally 12 months follow up (subjects will be consented for a maximum follow up of 5 years in case there are reasons that would require the follow up to be extended beyond the currently planned 12 months follow up).
Inclusion Criteria	1. Individual is ≥20 and ≤80 years old at time of enrollment (consent). 2. Individual has an office systolic blood pressure (SBP) ≥ 150 mmHg and <180 mmHg and an office diastolic blood pressure (DBP) ≥90 mmHg measured at Screening Visit 2, according to the guidelines in **Appendix 16.5**. 3. Individual has a valid 24-hour ABPM average SBP ≥140 mmHg and <170 mmHg measured at Screening Visit 2, according to guidelines in **Appendix 16.5**. ABPM is considered valid if the number of successful daytime readings captured is ≥ 21 and the number of successful nighttime readings captured ≥12. 4. Individual agrees to have all study procedures performed, and is competent and willing to provide written, informed consent to participate in this clinical study. 5. Individual is willing to discontinue current antihypertensive medications at Screening Visit 1 through the 3-month post-procedure visit.
Exclusion Criteria	1. Individual has one or more of the following conditions: stable or unstable angina within three months of enrollment, myocardial infarction within three months of enrollment; heart failure, cerebrovascular accident or transient ischemic attack, or atrial fibrillation at any time. Subjects are permitted to take aspirin or clopidogrel for cardiovascular risk reduction. Subjects who received catheter or surgical treatment for atrial fibrillation and are in sinus rhythm are not excluded. 2. Individual has undergone prior renal denervation. 3. Individual has at least one main renal artery with a diameter of less than 3 mm or greater than 8 mm.

	4. Individual has presence of FMD (defined as visible beading of the artery on angiography). 5. Individual has >50% stenosis in any treatable vessel. 6. Individual has a renal artery stent placed <3 months prior to the denervation procedure. 7. Individual has presence of a renal artery aneurysm defined as any localized increase in the diameter of the vessel. 8. Individual has disease not allowing any treatment in the main renal artery. 9. Individual has an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m^2, using the 4-variable MDRD calculation (in mL/min per 1.73 m^2 = 175 x SerumCr$^{-1.154}$ x age$^{-0.203}$ x 1.212 (if subject is black) x 0.742 (if female)). 10. Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%. (If the glycosylated hemoglobin in the subject's records is >3 months old (from the date of Screening Visit 2), or history of uncontrolled blood sugars raises concern, it is required to analyze glycosylated hemoglobin as part of Screening Visit 2 labs). 11. Individual is taking SGLT2 inhibitor or GLP-1 agonists that have been prescribed <90 days prior to Screening Visit 1 or does not plan on remaining on these drugs for the duration of the trial. 12. Individual has had [3] 1 episode(s) of orthostatic hypotension not related to medication changes within the past year or has had a reduction of SBP ≥20 mmHg or DBP ≥10 mmHg within three minutes of standing coupled with symptoms during the screening process (at SV2). 13. Individual requires chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea (e.g., CPAP, BiPAP). 14. Individual with a history of narcotic drug abuse, is currently on methadone, or who has used narcotic drugs more than once in the month prior to Screening Visit 1. 15. Individual had documented primary pulmonary hypertension.

	16. Individual has untreated secondary cause of hypertension (either known or suspected) or is taking drugs that increase sympathetic tone that could contribute to hypertension. 17. Individual has frequent intermittent or chronic pain that results in treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for two or more days per week over the month prior to Screening Visit 2. 18. Individual with HIV on anti-retroviral drug therapy without documentation that hypertension preceded initiation of anti-retroviral drug treatment. 19. Individual has a scheduled or planned surgery that, in the opinion of the Investigator, may affect study endpoints. 20. Individual has a documented condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the protocol-specified automatic/office blood pressure monitor (e.g., upper arm circumference outside cuff size ranges available by geography or arrhythmia such as atrial fibrillation that interferes with automatic monitor's pulse sensing and prohibits an accurate measurement). 21. Individual works night shifts. 22. Individual has severe cardiac valve stenosis for which, in the opinion of the investigator, a significant reduction of blood pressure is contraindicated. 23. Individual has a documented confounding medical condition, which in the opinion of the investigator, may adversely affect the safety of the participant (e.g., has clinically significant peripheral vascular disease, aortic aneurysm, bleeding disorders such as thrombocytopenia, hemophilia, or significant anemia). 24. Individual is pregnant, nursing or planning to become pregnant during the course of the study follow up. (Note: Pre-menopausal female participants must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test prior to angiography). 25. Individual has a known unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable, in the opinion of the investigator, to comply with study follow-up requirements.

	26. Individual is currently enrolled in a concurrent investigational drug or device study, unless approved by the study sponsor. (Note: For the purpose of this protocol, participants involved in extended follow-up studies for products that were investigational but are currently commercially available are not considered enrolled in an investigational study). 27. Individual is currently taking anti-mineralocorticoid drugs. (Note: Subjects may be enrolled as long as anti-mineralocorticoid drugs are weaned off at least 8 weeks prior to Screening Visit 1). 28. Individual has an active peptic ulcer or gastrointestinal (GI) bleeding within the prior six months from consent. 29. Individual has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions. 30. Individual has polycystic kidney disease, unilateral kidney, atrophic kidney, or history of renal transplant.
Follow up	Subjects will be followed up for a minimum of 12 months post-procedure (Subjects will be consented for a maximum of 5 years follow up).

Table 1: Schedule of Treatments and Assessments

	Screening			Procedure		Post-procedure follow up								
Required Assessments	**SV1**	**2Wk**	**SV2**	**Procedure**	**DC**	**2Wk**	**1M**	**6Wk**	**8Wk**	**10Wk**	**3M**	**4M[1]**	**6M**	**12M**
Mode (O- in office, P-phone)	O	O	O			O	O	P[2]	P[2]	P[2]	O	O	O	O
Window (M-month, Wk-week, d-days)	--	±3 d			--	±3 d	±7 d	±3 d	±7 d	±3 d	±14 d	±7 d	±14 d	±30 d
Medical history	X													
Clinical assessment		X	X			X	X				X	X[8]	X[8]	X[8]
Renal denervation procedure				X										
OBP per study guidelines	X	X	X		X	X	X	X[4]	X[4]	X[4]	X	X	X	X
24h ABPM per study guidelines			X								X		X	X
Witnessed pill intake[3]													X	X
Medications prescribed[1]											X[1]			
Blood tests (Chem7)[4]			X		X		X				X		X	X
Serum or urine pregnancy test			X											
Drug testing			X								X			
Renal artery imaging– angiogram				X										
Renal artery imaging-DUS[5]													X	
Mortality assessment[6]						X	X	X	X	X	X	X	X	X
Medication and event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]

1: 4M follow-up is only required if 3M systolic OBP≥140 mmHg, prescribe AH medications according to **section 9.1.9** if SBP ≥ 140 mmHg

2: If medically necessary, phone contact may be replaced with office visit. OBP (per **Appendix 16.5**) to be obtained for an office visit or following alternative methods of data collection as described in **section 9.1.6**.

3: Witnessed pill intake (if subject is taking AH medications), complete after OBP measurements

4: Bicarbonate will not be measured for subjects enrolled in Europe.

5: DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CT or angiogram to be used if DUS is nondiagnostic. Renal angiography must be used if repeat DUS/CTA/MRA is nondiagnostic or stenosis >60-70% is suspected. If renal imaging is not captured at the 6M follow-up visit due to extenuating circumstances, renal imaging is required at the next scheduled study visit.

6: Mortality assessment will be completed by the investigational site when a subject cannot be reached after each of the protocol required follow-up visits

7: SAE only review required at 12M visit

8: Clinical assessment of weight only

Table 2: Schedule of testing through 12 months for subjects with office SBP ≥180 mmHg (confirmed via 2 sets of measurements) or escape via investigator discretion during off-medication period post-procedure

	Procedure		Post-Procedure						
Required Assessments	**Procedure**	**DC**	**2Wk**	**1M**	**6Wk**	**10Wk**	**3M**	**6M**	**12M**
Mode (O- in office, P-phone)			O	O	O	O	O	O	O
Window (M-month, Wk-week, d-days)	--	--	± 3 d	±7 d	± 3 d	± 3 d	± 14 d	± 14 d	± 30 d
OBP per study guidelines		X	X	X	X	X	X	X	X
Renal artery imaging[1]								X[1]	
Mortality assessment[2]			X	X	X	X	X	X	X
Medication and event review		X	X	X	X	X	X	X	X[3]

1: DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CT or angiogram to be used if DUS is nondiagnostic. Renal angiography must be used if repeat DUS/CTA/MRA is nondiagnostic or stenosis >60-70% is suspected. If renal imaging is not captured at the 6M follow-up visit due to extenuating circumstances, renal imaging is required at the next scheduled study visit.

2: Mortality assessment will be completed by the investigational site when a subject cannot be reached after each of the protocol required follow-up visits

3: SAE only review required at 12M visit

3. Introduction

3.1. Background

Chronic activation of the sympathetic nervous system (SNS) has been identified by preclinical and clinical literature as a common and key factor in disease states such as hypertension, heart failure, and chronic kidney disease.[1-3] The renal sympathetic nerves are a major contributor to the complex pathophysiology of elevated SNS activity and hypertension. Therapeutic renal denervation, the deliberate disruption of the sympathetic nerves connecting the kidneys with the central nervous system, has been shown to be an effective means of modulating elevated SNS activity - both by reducing the sympathetic control of renal function (renin release, sodium excretion and renal blood flow) and by removing the renal afferent sympathetic contribution to central sympathetic elevation.[4] It is important to note that the kidneys maintain appropriate electrolyte and volume homeostasis, despite being denervated, as demonstrated by the human kidney transplant experience.[5] Prior to pharmacological treatment, hypertension was sometimes treated with complex invasive procedures, such as surgical nephrectomy and even radical surgical sympathectomy.

Medtronic has developed a radiofrequency catheter with multiple electrodes, as a minimally invasive means of achieving renal sympathetic denervation. Bilateral renal denervation will be performed using a percutaneous, catheter-based system that delivers radiofrequency (RF) energy through the luminal surface of each renal artery at four locations simultaneously. In comparison to the previous single-electrode Symplicity™ renal denervation system, the multi-electrode catheter provides the physician with a pre-defined and consistent ablation pattern that is intended to improve the accuracy of treatment. The RF energy may be delivered to up to 4 electrodes simultaneously. If the physician elects to complete multiple treatments in one artery, subsequent treatments are easily accommodated by re-positioning the catheter proximally (at least 5 mm) and de-selecting electrodes via the graphical user interface on the Symplicity G3 generator. The electrodes are mounted on to a self-expanding Nitinol shaft that takes a spiral configuration allowing electrode contact with the vessel wall. An evaluation of the results of pre-clinical (*in-vivo*) and *in-vitro* testing supporting the use of the Symplicity Spyral catheter and Symplicity G3 generator as investigational devices in human subjects is included in the Investigator's Brochure. Medtronic has performed a comprehensive set of bench testing and preclinical studies that have shown that this manner of low-power ablation produces distinct, focal, sterile lesions that subsequently heal, resulting in no clinically relevant long-term sequelae to either the vessel or the kidney.

The currently ongoing SPYRAL PIVOTAL – SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED studies are multi-center, international, single blind, randomized, sham-controlled studies designed to evaluate the effect of renal denervation on blood pressure. The SPYRAL PIVOTAL – SPYRAL HTN-OFF MED study is evaluating the effect of renal denervation in the absence of antihypertensive medications, whereas the SPYRAL HTN-ON MED study is evaluating the effect of renal denervation on standard medical therapy.

Preliminary data on the first 80 randomized subjects with three months follow up within the SPYRAL HTN-OFF MED study were published in August 2017 in *The Lancet.*[6] The mean difference between the groups favored renal denervation for 3-month change in both office and 24-h blood pressure from baseline: 24-h SBP –5·0 mm Hg (95% CI –9·9 to –0·2; p=0·0414), 24-h DBP –4·4 mm Hg (–7·2 to –1·6; p=0·0024), office SBP –7·7 mm Hg (–14·0 to –1·5; p=0·0155), and office DBP –4·9 mm Hg (–8·5 to –1·4; p=0·0077). Baseline-adjusted analyses showed similar findings. There were no major adverse events in either group. Additionally, preliminary data on the first 80 randomized SPYRAL HTN-ON MED subjects with six months follow-up were published in May 2018 in *The Lancet.*[7] Office and 24-h ambulatory blood pressure decreased significantly from baseline to six months in the renal denervation group: 24-h SBP –7·0 mm Hg, 95% CI –12·0 to –2·1; p=0·0059, 24-h DBP –4·3 mm Hg, –7·8 to –0·8; p=0.0174, office SBP –6·6 mm Hg, –12·4 to –0·9; p=0·0250, and office DBP –4·2 mm Hg, –7·7 to –0·7; p=0·0190). The change in blood pressure was significantly greater at six months in the renal denervation group than the sham-control group for office SBP (difference –6·8 mm Hg, 95% CI –12·5 to –1·1; p=0·0205), 24-h SBP (difference –7·4 mm Hg, –12·5 to –2·3; p=0·0051), office DBP (difference –3·5 mm Hg, –7·0 to –0·0; p=0·0478), and 24-h DBP (difference –4·1 mm Hg, –7·8 to –0·4; p=0·0292).

These initial results from both studies provided biological proof of principle for the blood-pressure-lowering efficacy of renal denervation. The safety profile within these published cohorts showed no major adverse events.

In order to test the hypothesis in the SPYRAL PIVOTAL - SPYRAL HTN-OFF MED study that renal denervation decreases blood pressure and is safe when studied in the absence of antihypertensive medications, study subjects were randomized to the Denervation or Control group in a 1:1 fashion. In addition to subjects being blinded to their randomization assignment, site personnel involved in the measurement of office blood pressure were also blinded to study subjects' randomization assignment through the primary endpoint to prevent potential bias of results. Subjects were studied in the absence of antihypertensive medications to assess the impact of renal denervation on systolic blood pressure in the absence of medication.

Study enrollment was stopped for efficacy after the first interim analysis in February 2020. Data from the initial 80 patients with three months follow up from the SPYRAL HTN-OFF MED study was combined with data from the initial 251 patients with three months follow up from the SPYRAL PIVOTAL-SPYRAL HTN-OFF MED study and was presented at ACC World Congress of Cardiology in March 2020. Concurrently, an article presenting the data was published in *The Lancet*. A brief summary of the SPYRAL PIVOTAL-SPYRAL HTN-OFF MED data is provided below.

The primary endpoint, change in 24-h blood pressure at three months, was compared between groups. Drug surveillance was done to ensure patient compliance with absence of antihypertensive medication. The primary analysis was done in the intention-to-treat population. Safety events were assessed to three months.

From June 25, 2015, to Oct 15, 2019, 1519 patients were enrolled, of whom 1188 were excluded because they did not meet inclusion criteria. 166 were randomly assigned to renal denervation and 165 to the sham procedure (80 were included in the pilot and 251 in Pivotal).

There were no major safety events reported at one month. There was one major safety event in each treatment group up to three months (one admission to hospital for hypertensive crisis or emergency in the renal denervation group and one new stroke in the sham procedure group), and neither was attributed to the device or trial procedures.

For the primary efficacy endpoint of changes from baseline in 24-h systolic blood pressure at three months, there was a significant difference between the renal denervation and sham procedure groups. This endpoint was met with a posterior probability of superiority greater than 0.999 and a treatment difference of -3.9 mm Hg (95% BCI -6.2 to -1.6)**.** For the secondary efficacy endpoint of difference in three-month changes in office systolic blood pressure between the two groups, the difference was significant, and the endpoint was met (difference -6.5 mm Hg (95% BCI -9.6 to -3.5), with posterior probability of superiority of more than 0.999**.** The blood pressure changes analyzed using the prespecified ANCOVA-adjusted frequentist analysis of the overall population show similar changes in blood pressure to Bayesian results.

Besides the "confounding factors" analysis of SYMPLICITY HTN-3[8] indicating that the blood pressure response to renal denervation may depend on the number of lesions applied, few studies have shown a strong relationship between the number of lesions delivered and subsequent blood pressure reduction. These new results indicate that the location of the lesion, i.e., the distal main and branches, may be an important factor in blood pressure reduction.

Both SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED trials used the same RDN technique, applying treatments in eligible renal arteries and the branches, and presented similar results in three and six months follow-up, respectively. In the SPYRAL HTN-OFF MED[6] trial, on average 17.9 ± 10.5 ablations were performed in the main renal arteries, and an additional 25.9 ± 12.8 ablations were performed in branch vessels.

Recently Petrov and colleagues[9] evaluated renal denervation therapy beyond the proximal main renal artery (Y-pattern), including the primary branches, and compared it to the standard procedure applied only within the main vessel. In 80 patients treated with the standard ablation using the first generation Symplicity "Flex" catheter, 12.0± 3.0 total ablations (both sides) were applied while 20.4±3.9 total ablations were delivered for the group of 39 patients with Y-pattern denervation ($P < 0.001$). Renal denervation was associated with significant decreases in both office and ambulatory systolic and diastolic blood pressure in both groups. The reduction in 24-hour mean ambulatory systolic blood pressure at six months was significantly greater ($P = 0.002$) for the Y-Pattern group (−22.1 ± 15.4 mm Hg) compared to the Standard group (−11.8 ± 16.2 mm Hg). Changes in diastolic office and ambulatory pressure were also

significantly greater at six months in the Y-pattern ablation group. These findings support the benefit of improved blood pressure reduction by including denervation of nerves in the renal artery branch vessels.

Similarly, Pekarskiy and colleagues[10] compared renal denervation therapy in the distal main vessel and the arterial branches to ablation in the proximal main artery in 51 randomized hypertensive subjects. The magnitude of the 24-hour pressure drops at six months post-procedure for the "distal" approach was significantly higher than the "traditional" approach achieved using the Symplicity Flex denervation system (22.6 ± 20.0 vs 9.4 ± 18.7 mm Hg; $P < 0.05$).

In a dual-center prospective analysis, Fengler and colleagues[11] reported comparative efficacy and safety between a group of 25 treatment resistant hypertension patients treated with ablation of main renal artery, side branches, and accessory arteries to a matched control group (N = 25) with only main renal artery ablation. Systolic 24-hour mean ABP decreased significantly after three months in the combined ablation group (−8.5 ± 9.8/−7.0 ± 10.7 mm Hg, $P < 0.001/0.003$), but not in patients with main artery treatment (−3.5 ± 11.1/−2.0 ± 7.6 mm Hg, $P = 0.19/0.20$) and systolic daytime BP was significantly lower in patients with combined ablation compared to main artery ablation ($P = 0.033$).

The results of the preclinical IVY study using norepinephrine drop and cortical axon area density as alternative indices to blood pressure drop when main vessel ablation was augmented with branch therapy treatment in a long-term study in pigs[13] also shows a trend towards greater office blood pressure reduction.

A post hoc analysis of a previously reported single center non-randomized study from Kiuchi and colleagues[14] analyzed the correlation between the number of lesions and blood pressure drop according to lesion location supporting the concept of targeting the distal part of the main renal artery and the branches rather than increasing the number of RF applications in the main renal artery. Thirty patients with "resistant" hypertension and CKD received renal denervation with a cardiac EP catheter. Mean 24-hour systolic blood pressure decreased by 21 mmHg at two years. An average of 17 total lesions (right plus left) were applied, including an average of 5 proximal, 5 mid, 5 distal, and 2 branch lesions. The total number of ablations was not correlated with BP drop. However, the number of lesions applied in the branches was linearly associated with 24-hour SBP-lowering effect at both 12 and 24 months of follow up. The strongest correlation between the number of lesions and blood pressure drop was observed when combining distal main plus branch lesions. The results suggest that focusing therapy on the distal main and branches may increase blood pressure reduction.

Besides one HTN-3 post hoc analysis,[8] no trial (including SPYRAL HTN-ON and -OFF MED) has shown a correlation between the total number of lesions and BP reduction. The number of RF lesions did not correlate with BP reduction,[15-19] unless the lesions were delivered to the branches.[14,20]

As compared to the currently recommended procedure specified in the SPYRAL HTN ON and OFF MED trials, a procedure focused on the distal main renal arteries and first order branches suggests similar safety

and blood pressure reductions but with potential for shorter procedural times, less radiation exposure, and less contrast usage.

3.2. Purpose

The objective of this single arm interventional study is to determine if renal denervation performed in the distal main renal arteries and first order branches is as effective as the procedural approach in the SPYRAL HTN-OFF MED clinical study.

4. Objectives and Endpoints

4.1. Objectives

The objective of this single arm interventional study is to determine if renal denervation performed in the distal main renal arteries and first order branches is as effective as the procedural approach in the SPYRAL HTN-OFF MED clinical study.

4.2. Endpoints

The following endpoints will be analyzed in this study:

4.2.1. Efficacy endpoints

The efficacy endpoints will be compared to the SPYRAL HTN-OFF MED efficacy endpoints using a propensity score stratified analysis at 3 months. At 6 months and 12 months, the endpoints will be compared and analyzed within the SPYRAL DYSTAL study only.

- Change in systolic blood pressure (SBP) from baseline (Screening Visit 2) to 3, 6, and 12 months post-procedure as measured by 24-hour ABPM.
- Change in office SBP from baseline (Screening Visit 2) to 3, 6, and 12 months post-procedure.
- Change in diastolic blood pressure (DBP) from baseline (Screening Visit 2) to 3, 6, and 12 months post-procedure as measured by 24-hour ABPM.
- Change in office DBP from baseline (Screening Visit 2) to 3, 6, and 12 months post-procedure.
- Incidence of achieving target office SBP (SBP<140 mmHg) at 3, 6, and 12 months.
- Compare the pattern of BP reduction over 24 hours of ABPM between this study and the SPYRAL HTN-OFF MED study.

4.2.2. Safety endpoints

- Composite safety endpoint at 1, 3, 6, and 12 months post-procedure:
  Incidence of the following events:
  - All-cause mortality
  - End-stage renal disease (ESRD)
  - Significant embolic event resulting in end-organ damage
  - Renal artery perforation requiring intervention
  - Renal artery dissection requiring intervention
  - Vascular complications

- Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol
- New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core lab at 6-months follow up

- Myocardial infarction
- Stroke
- Renal artery re-intervention
- Major bleeding according to TIMI definition (i.e., intracranial hemorrhage, ≥5 g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within seven days of the procedure)
- Increase in serum creatinine >50% from Screening Visit 2

4.2.3. Additional analysis

The following additional analyses will be conducted:

- Comparison of procedural characteristics, such as total procedure duration, denervation time but not limited to that, between SPYRAL DYSTAL and SPYRAL HTN-OFF MED

5. Study Design

The SPYRAL DYSTAL study is a multi-center, international, prospective, interventional, single-arm study designed to study renal denervation in the distal portion of the main renal arteries and first-order branches. Denervation will be performed using the Symplicity Spyral multi-electrode renal denervation catheter (Symplicity Spyral catheter) and the Symplicity G3 renal denervation radio frequency (RF) generator in a hypertensive population. Subjects will be studied to assess the impact of this renal denervation approach on systolic and diastolic blood pressure.

The Symplicity Spyral catheter and Symplicity G3 generator provide a spiral pattern of denervation, ensuring circumferential nerve ablation, which is expected to minimize procedure variability. One Symplicity G3 generator is intended to be used with a Symplicity Spyral catheter in enrolled subjects. Subjects will be studied in the absence of anti-hypertensive medications through the 3-month visit to assess the impact of renal denervation on blood pressure in the absence of medications.

Based on previous experience with the SPYRAL HTN-OFF MED study, it is anticipated that there will be subjects who will no longer meet study eligibility during the screening period; therefore, approximately 350 subjects will be enrolled to ensure approximately 50 hypertensive subjects will undergo the renal denervation procedure at up to 15 sites. Once enrolled, subjects will undergo screening visits and if eligible, will undergo renal denervation and will be followed for at minimum 12 months post-procedure. Follow-up visits will take place at discharge, 2Wk, 1M, 6Wk, 8Wk, 10Wk, 3, 4 (if applicable), 6, and 12 months (see **Table 1** for treatments and assessments that will occur at each visit). Upon completion of all follow-up visits, subjects will be exited from the study. Subjects will be consented for a maximum follow-up of 5 years in case there are reasons that would require the follow up to be extended beyond the currently planned 12-months follow up.

The following procedures are defined as outside of Standard of Care CIP procedure (applicable as of EU MDR Date of Application) any time they are conducted as per the schedule of events outlined in the CIP:

- Study requirement for subjects to be off antihypertensive medication until the 3-month visit.
- Medication re-introduction
- Office Blood Pressure
- 24-hour Ambulatory Blood Pressure Monitoring (ABPM), except in several EU countries
- Blood tests
- Procedural angiogram (renal artery imaging – angiogram)
- Follow-up Duplex Ultrasound imaging (DUS) (renal artery imaging)

- Follow-up Magnetic Resonance imaging (MRA) (renal artery imaging)
- Follow-up Computerized Tomographic imaging (CTA) (renal artery imaging)

5.1. Duration

Subjects will participate in the study from the time of signing consent (defined as enrollment) until study exit or the time of completion of at least 12 months of follow up post-procedure (subjects will be consented for a maximum follow-up of 5 years in case there are reasons that would require the follow up to be extended beyond the currently planned 12-months follow up).

Enrollment is expected to take approximately 12 months. Individual investigational sites may enroll up to 20% of the total study subjects. Total study duration is expected to take approximately 2.5 years.

5.2. Rationale

5.2.1. Rationale for duration of period off medications

A review of hypertension studies of antihypertensive medications was undertaken in conjunction with a thorough review of the SYMPLICITY HTN-3 data. Based on this, Medtronic plans to follow the accepted pharmaceutical model for hypertension studies and utilize a washout period. This will involve a three to four week washout period free of antihypertensive medications prior to procedure, followed by a 12 week post-procedure period off medication. Washout and discontinuation of antihypertensive medications during the off-medication period should eliminate medication adherence concerns and address both lack of adherence and medication changes as potential confounding factors identified in SYMPLICITY HTN-3.

Inclusion and exclusion criteria traditionally used in pharmaceutical studies[18] will be utilized as they have historically ensured that only subjects with true hypertension (vs white coat) are included and also ensure that these subjects are not borderline hypertensive (ambulatory SBP close to 135 mmHg and office SBP close to 140 mmHg). Subjects will undergo regular office visits that include blood pressure measurement to ensure safety during the off-medication period.

5.2.2. Rationale for comparator

The efficacy endpoints in this study will be compared to the SPYRAL HTN-OFF MED efficacy endpoints using a propensity score stratified analysis as outlined in **section 13.4**.

The SPYRAL HTN-OFF MED study was chosen because this study has the same eligibility criteria as the SPYRAL DYSTAL study, except for the anatomical exclusion criteria. The studies both evaluate blood pressure response after approximately 4-months off medication period (office BP and ABPM) post-

procedure. The SPYRAL HTN-OFF MED and the SPYRAL DYSTAL studies have different procedural requirements which allows for comparison of blood pressure reductions between the two studies.

6. Product Description

6.1. The Symplicity Spyral™ multi-electrode renal denervation system

The Symplicity Spyral multi-electrode renal denervation system (Symplicity Spyral catheter and Symplicity G3 generator) is comprised of a single use, disposable catheter, and a reusable radiofrequency (RF) generator. The intended use is to deliver low-level radiofrequency energy through the wall of the renal artery to denervate the human kidney. The Symplicity Spyral catheter and Symplicity G3 generator received CE Mark in October 2013 and has been commercially available in selected geographies.

6.2. The Symplicity Spyral™ Catheter

The Symplicity Spyral catheter when used with the Symplicity G3 generator will allow for rapid treatment of renal arteries by simultaneously delivering radiofrequency energy to four electrodes. The Symplicity Spyral catheter consists of a distal, self-expanding array of four gold electrodes radially spaced by approximately 90 degrees in a spiral configuration (**Figure 1**). To minimize the thermal effects on the renal artery wall, the design allows for continuous blood flow throughout the treatment, allowing cooling of the artery wall and electrodes during treatment. The catheter is advanced to the treatment site by tracking over a 0.014 inch guidewire using a rapid exchange based catheter system (**Figure 2**). The proximal end of the guidewire is inserted through the spiral flexible array via the straightening tool, reducing the system into a low-profile straight configuration that is 6F compatible and ready for delivery to the renal artery treatment site. A radiopaque marker is embedded in the catheter approximately 1 mm proximal from the tip to assist in the positioning of the catheter using fluoroscopic guidance. After the device is placed in a desired position for ablation in accordance with the IFU, the guidewire is retracted proximally to allow the pre-shaped nitinol spiral electrode array to expand radially and place the electrodes in contact with the arterial wall in a spiral pattern. The Symplicity Spyral catheter is designed to attain acceptable electrode-vessel positioning and wall contact with less overall manipulation and/or interpretation as compared to the single-electrode Symplicity catheter design. After treatment, the guidewire can be advanced distally to straighten the electrode array and allow for removal from the vessel into the guide catheter for placement into the contra-lateral renal artery where the treatment procedure is repeated.

Figure 1: Spiral Configuration of Four Gold Electrodes

The self-expanding electrode array consists of nitinol stranded tubing to maintain spiral shape-set and guidewire lumen integrity during the procedure. The gold electrodes are placed over a polymer outer cover that provides insulation from nitinol tubing and bi-filar wires that deliver the RF energy and measure temperature. The proximal end of the self-expanding electrode array assembly is attached to the intermediate shaft assembly. The intermediate shaft assembly balances the flexibility between the proximal shaft and electrode array assembly. The intermediate shaft assembly contains a guidewire lumen that terminates at the rapid exchange (RX) guidewire exit port. The jacketed proximal stainless steel hypotube joins the delivery system to the handle and integrated cable. The cable connector connects directly into the Symplicity G3 generator.

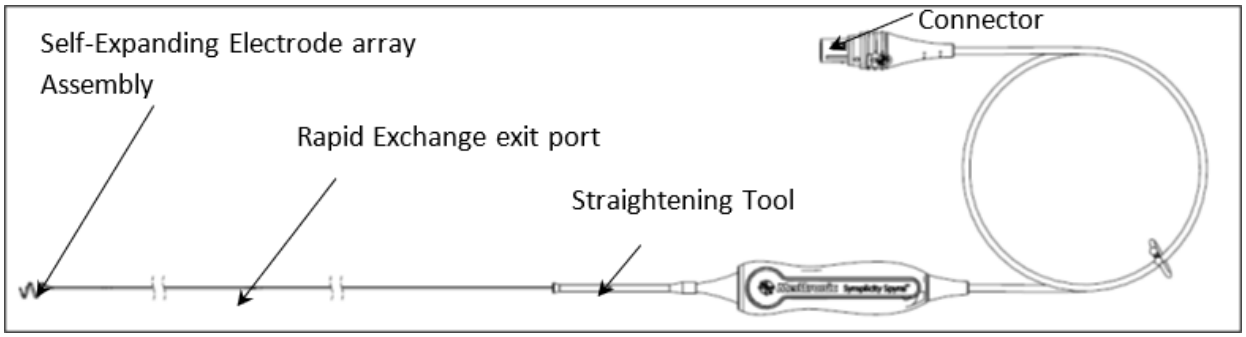

Figure 2: Overview of Symplicity Spyral™ Catheter

The electrodes in the multi-electrode spiral arrangement are positioned to cover all four quadrants of the artery's circumference. The catheter is for single-use only and is sterilized by E-beam irradiation. It is provided in a hooped configuration within a tray sealed with a coated Tyvek® lid.

6.3. Symplicity G3™ Generator

The Symplicity G3 generator (see **Figure 3**) is intended to provide a safe and effective means of delivering RF energy to the Symplicity Spyral catheter for controlled ablation of tissue. The Symplicity G3 generator has been designed with the following features:

- Automated safety algorithms similar in all aspects of safety and energy delivery and stoppage to first generation Symplicity RF generator
- Non-adjustable treatment parameters
- System performance self-checks at power on and during system operation
- Simultaneous firing of all four electrodes
- Option to select/deselect electrodes per physician discretion
- Touch-screen interface, which allows the user to individually select or de-select the electrodes
- Internal RFID tag within the Symplicity Spyral catheter, to communicate with an RFID antenna located inside the Symplicity G3 generator to ensure the catheter cannot be re-used
- Messages and audible indicators to the operator with system status information including treatment application, warning indications and error indication
- Universal power supply
- Remote as optional component allowing extension of user interface

Figure 3: Symplicity G3™ Generator

Treatments are initiated by an operator using an optional foot switch, remote control, or a button on the front of the generator and may also be manually stopped by the operator using these same methods. Default treatment parameters cannot be changed by the operator.

Monopolar RF energy is delivered through each electrode, requiring the use of a dispersive electrode to provide a return path for currents exiting the catheter. Temperature and impedance values are monitored

at each electrode and used to provide input to an algorithm controlling power delivery for individual electrodes (**Figure 4**).

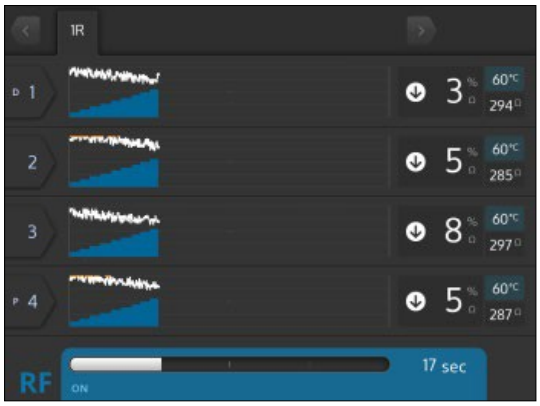

Figure 4: RF on Screen

The following ancillary components may be used with the Symplicity G3 generator:

- Symplicity G3 generator cart - an optional accessory as a convenience to facilitate movement of the generator within the operating room. The generator cart may be provided as part of the clinical study in applicable geographies.
- Foot switch
- Digital Visual Interface (DVI-D) cable - enables the user to extend the visual display of the Symplicity G3 generator user interface to standard monitors within the cath lab
- Wired remote control - enables the user to control the generator from within the sterile field

6.4. Manufacturer

The Symplicity Spyral catheter is manufactured at Medtronic Ireland. The Symplicity G3 generator (and ancillary components) is manufactured by Plexus Corp. (Pinnacle Hill, Kelso TD5 8XX, UK) for Medtronic.

6.5. Packaging

The Symplicity Spyral catheter and Symplicity G3 generator will include the following labeling information in geographies where the product is not commercially available:

- That the device is intended for investigational use in geographies where the product is not approved.
- Identification Number
- Model number

- Lot/Serial number
- Storage condition
- Expiration date
- Name and address of sponsor

An *Instructions for Use (IFU)* document is included with each Symplicity Spyral catheter and a *User Manual* is included with each Symplicity G3 generator.

6.6. Intended Population

The Symplicity Spyral catheter and Symplicity G3 generator are indicated for the treatment of uncontrolled hypertension.

6.7. Equipment

Medtronic will be responsible for maintenance of the Symplicity G3 generator. In addition, the calibration of the office blood pressure (OBP) machines and ambulatory blood pressure machines (ABPMs) will be done by Medtronic according to the manufacturer's requirements. Documentation of the routine maintenance will be provided to the study site upon completion.

6.8. Product Use

The Symplicity Spyral catheter and Symplicity G3 generator should be used as outlined in the IFU.

Medtronic has performed a comprehensive set of bench testing and preclinical studies that have shown that the manner of low-power ablation produces distinct, focal, sterile lesions that subsequently heal, resulting in no clinically relevant long-term sequelae to either the vessel or the kidney. The ability to denervate using this approach has been demonstrated to effectively reduce renal nerve activity.

Preclinical studies and histological analyses[8-10] observed that renal nerves may have a positional bias, suggesting the distal nerves are closer to the arterial lumen (**Figure 5**). Targeted renal ablation in the distal main and branches of the renal arteries may increase the amount of nerve ablation and decrease the variability of denervation response.

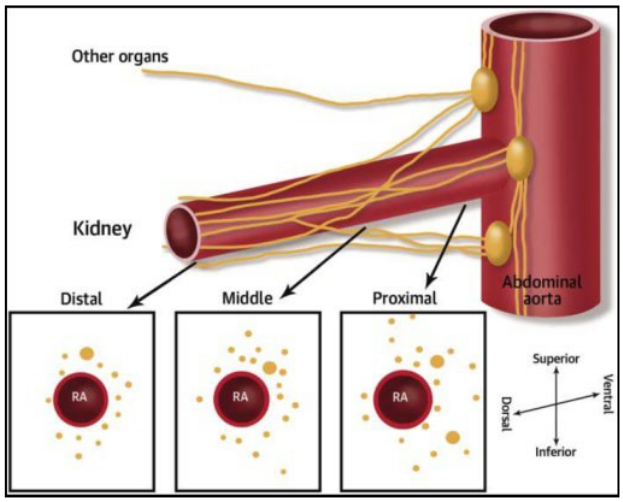

Figure 5: Illustration of peri-arterial renal nerve location

Initial clinical evidence[11] from commercial experience supports the combination of branch and main renal artery treatments providing a larger and more consistent decrease in blood pressure while maintaining the safety profile of renal denervation that was previously established. Treatment of the distal main renal arteries and first-order branches will be evaluated in this clinical study to confirm the safety and efficacy of this approach.

The catheter is introduced percutaneously to the renal artery via a commercially available sheath and 6F guiding catheter suitable for renal artery intervention, using the femoral artery as the access site. A 6F sized commercially available guide catheter and a commercially available hemostatic introducer sheath may be used in the placement of the catheter. The treatment involves the delivery of a relatively low-power and precisely focused RF energy of up to 6.5W to each electrode, simultaneously through the wall of the renal artery to disrupt the surrounding renal nerves. The low-power RF ablation has been shown to effectively disrupt the renal nerves (located in the adventitia of the renal artery, as depicted in **Figure 6**) without adversely affecting the wall of the artery or surrounding organs.

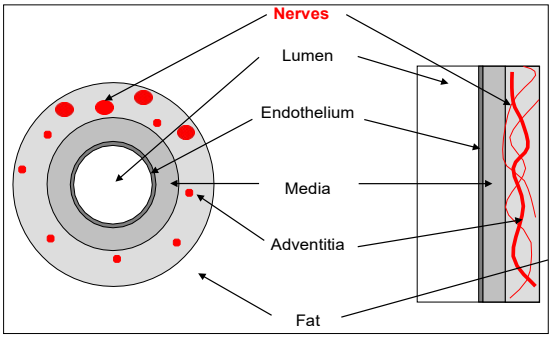

Figure 6: Illustration of renal artery anatomy

6.9. Product Training Requirements

The training approach for the SPYRAL DYSTAL study is described below.

All participating sites in this study will have previous experience with the Symplicity Spyral multi-electrode renal denervation system.

Investigators will be trained on the protocol, the procedural approach (as applicable) and other topics related to the procedure prior to starting study-related activities. If a participating proceduralist has prior experience with using the Spyral catheter, no further (online) training is required.

An online training will be set up on a dedicated learning website for proceduralists with limited experience only and is required to be completed before the interventionalist will attend the investigator training meeting. The goal for the online training is to provide investigators with an understanding of the handling of the Symplicity catheter and Symplicity G3 generator before coming to the meeting. The progress of each investigator will be reviewed and documented in the specific training files (site and sponsor). The topics for the online training will include but are not limited to following topics:

- Review of Spyral In-service Slide deck
- Review of recorded Spyral cases

In the event of a delay greater than three months between the investigator training and the first case performed by an investigator, or more than three months between cases during the trial, a refresher shall be performed. This will be accomplished by visiting the online training platform and reviewing a recorded case, together with potential other tasks.

6.10. Product Receipt and Tracking

Sites are required to maintain investigational device records that contain the following information on all components shipped to the site for the study:

- Investigational device name
- Device serial/model number
- Date of receipt of device
- Name of person receiving the device
- Name of person using/opening the device (if applicable)
- Date of use (if applicable)/expiration date
- Subject Identification Number (SID) of subject receiving or using the device (if applicable)
- Disposition (implanted, disposed of, or returned to Medtronic)

For devices that are returned to Medtronic or disposed of, sites are required to document the following additional information:

- The reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date shipped to Medtronic, if returned
- If device is disposed of, the method of disposal

At the end of study enrollment, all remaining investigational devices must be returned to Medtronic.

The Symplicity Spyral catheter and Symplicity G3 RF generator are commercially available in countries that accept CE-mark and will be used within approved labelling for this study. The Symplicity Spyral catheter and Symplicity G3 RF generator are investigational in the US.

The following devices will be provided to sites and must also be tracked during the clinical study:

- Office blood pressure monitors
- Ambulatory blood pressure monitors

6.11. Product Storage

The Symplicity Spyral catheter and Symplicity G3 generator must be stored as labeled at all sites.

Investigational devices/products or products provided by Medtronic free of charge must be stored in a secured area. The method of storage shall prevent the use of investigational devices/products for other applications than mentioned in this clinical investigation plan (CIP). In addition, all information for the use, storage and handling of the investigational device/product as indicated in the *IFU* and *User Manual* must be taken into account.

6.12. Product Return

Non-functioning investigational devices must be returned to Medtronic as soon as possible for investigation. If a Symplicity G3 generator or Symplicity Spyral catheter needs to be returned (e.g. expired), a Medtronic representative will help facilitate the return and provide a return address and local procedures that need to be followed. In case a Symplicity G3 generator or Symplicity Spyral catheter needs to be returned, it will be returned to the address below, following local procedures:

Symplicity G3 generator:

Medtronic CardioVascular
Service and Repair
Attn: RMA#_____
Service & Repairs
7611 Northland Drive
Brooklyn Park, MN 55428
Tel: +1 800-433-4311

Symplicity Spyral catheter:

Medtronic PXM RGI Lab Building 4
Parkmore Business Park West
Ballybrit
Galway
H91 A2Y5
Ireland

At the end of the clinical study, all remaining investigational devices/products must be returned to Medtronic in the applicable region.

7. Ethics

7.1. Statement(s) of Compliance

This study is designed to reflect the good clinical practice (GCP) principles outlined in the latest version of ISO 14155. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators.

The study will also be conducted in accordance with the Declaration of Helsinki. The principles of the Declaration of Helsinki (2013) are implemented in this study by means of the Patient Information and Informed Consent (IC) process, Ethics Committee approval, study training, clinical study registration, pre-clinical testing, risk benefit assessment, and publication policy. This clinical study will also be registered on clinicaltrials.gov and study results posted based on the posting rules stipulated.

In addition, the study will be conducted in compliance with the latest version of ISO 14155, EU MDR and other local regulatory requirements as applicable, will also be followed. As the ISO 14155 adverse event requirements are focused on pre-market release studies, the adverse event collection will be focused on collecting all adverse events only up to 6-months follow up (after that, only serious adverse events will be collected). The USADE assessment will also not be performed as the product is market-released in Europe.

In addition, laws and regulations of the countries in which the SPYRAL DYSTAL study is conducted, including data protection laws, will be followed.

21 CFR Part 56 (Institutional Review Boards), Part 50 (Protection of Human Subjects), and Part 812 (Investigational Device Exemptions) only apply to the US; not to other geographies.

Regulatory authority notification/approval to conduct the study is required in all participating geographies (where applicable). Investigational sites will be not be activated, nor begin enrolling subjects until the required approval/favorable opinion from the respective regulatory agency has been obtained (as appropriate). The clinical investigation shall not begin until the required approval/favorable opinion from the ethics committee (EC) / institutional review board (IRB) or notification/approval from a regulatory authority have been obtained. Additionally, any requirements imposed by a local regulatory agency or EC/IRB shall be followed, as appropriate.

Each site must provide Medtronic with a copy of the investigational site's EC/IRB approval letter and the EC/IRB-approved Patient Information and Informed Consent form.

If applicable, approvals for the continuation of the study at each investigational site must be kept current in accordance with the EC/IRB review schedule. All site communications to and from the EC/IRB must be forwarded to Medtronic as they are sent/received.

The sponsor will be informed by the EC/IRB and/or the investigator in case any action is taken by an EC/IRB with respect to this investigation.

Study reimbursement is outlined in the clinical trial agreement. Indemnification will be done according to local laws.

Medtronic contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic

This study will be publicly registered on www.clinicaltrials.gov prior to first enrollment. This study will not start enrollment in a geography unless applicable national regulatory approval for the Symplicity Spyral catheter and G3 generator have been obtained. The devices should be used within the intended approved indication.

7.1.1. Ethics Committee/Institutional Review Board Approval

Here and throughout the document, "EC/IRB" is the term that will be used collectively in reference to an ethics committee (EC), institutional review board (IRB), medical ethics committee (MEC), human research ethics committee (HREC), research ethics board (REB) unless otherwise stated.

Prior to enrolling subjects in this clinical study, each investigational site's EC/IRB will be required to approve the current CIP, the Patient Information and Informed Consent form, including any other written information to be provided to the subjects and, if applicable, the Investigator's Brochure.

EC/IRB approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigational site. The approval letter must contain the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an EC/IRB roster or letter of compliance, to allow verification that the investigator, other investigational site personnel, and/or Medtronic personnel are not members of the EC/IRB. If they are members of the EC/IRB, written documentation is required stating that he/she did not participate in the approval process. If the EC/IRB imposes any additional requirements (e.g., safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the investigator for reporting to the EC/IRB. Investigators must inform Medtronic of any change in status of EC/IRB approval once the investigational site has started enrollment. If any action is taken by an EC/IRB with respect to the clinical study, that information will be forwarded to Medtronic by the respective investigator.

Medtronic may revise the CIP, IB (if applicable), IFU, CRFs, Patient Information and Informed Consent form and other study documents during the study when revision(s) is determined necessary. Medtronic will submit revisions to the regulatory authorities (if applicable per local regulation) and will also request that sites submit to their EC/IRB for review per national and local requirements.

7.1.2. Regulatory Submission

In countries where submission to the regulatory authority is required per local law, no subjects will be enrolled in the clinical study until the respective regulatory authority has approved the current CIP or subsequent amendments for the clinical study and other documents as required according to the local requirements.

If the regulatory authority imposes any additional requirements (e.g., safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority (as applicable).

8. Selection of Subjects

8.1. Study Population

The population eligible for inclusion into this study includes subjects with uncontrolled hypertension in accordance with the Inclusion and Exclusion criteria specified in the protocol.

8.2. Subject Enrollment

Subjects will be pre-screened for potential enrollment in the clinical study based on prior medical history and records of office systolic blood pressure.

A subject is considered enrolled in this clinical study at the time at which the subject and investigator or authorized designee have personally signed and dated the Patient Information and Informed Consent Form. Written informed consent must be obtained prior to Screening Visit 1.

Investigational sites will maintain a subject identification log; however, this document will not be submitted to the sponsor.

It is anticipated to enroll approximately 350 subjects to reach approximately 50 renal denervation treated subjects within this study.

Each site will receive a supply of single-use catheters. A minimum of 50 single use catheters will be required to treat approximately 50 subjects. It is anticipated that a small number (<10%) of catheters will need to be replaced due to damage or contamination. Sites will be expected to return all unused study product to Medtronic.

8.3. Inclusion Criteria

1. Individual is ≥20 and ≤80 years old at time of enrollment (consent).
2. Individual has an office systolic blood pressure (SBP) ≥150 mmHg and <180 mmHg and an office diastolic blood pressure (DBP) ≥90 mmHg measured at Screening Visit 2, according to the guidelines in **Appendix 16.5**.
3. Individual has a valid 24-hour ABPM average SBP ≥140 mmHg and <170 mmHg measured at Screening Visit 2, according to guidelines in **Appendix 16.5**.

   ABPM is considered valid if the number of successful daytime readings captured is ≥21 and the number of successful nighttime readings captured ≥12.
4. Individual agrees to have all study procedures performed, and is competent and willing to provide written, informed consent to participate in this clinical study.
5. Individual is willing to discontinue current antihypertensive medications at Screening Visit 1 through the 3-month post-procedure visit.

8.4. Exclusion Criteria

1. Individual has one or more of the following conditions: stable or unstable angina within 3 months of enrollment, myocardial infarction within 3 months of enrollment; heart failure, cerebrovascular accident or transient ischemic attack, or atrial fibrillation at any time. Patients are permitted to take aspirin or clopidogrel for cardiovascular risk reduction. Patients who received catheter or surgical treatment for atrial fibrillation and are in sinus rhythm are not excluded.
2. Individual has undergone prior renal denervation.
3. Individual has one or more main renal artery with a diameter of less than 3mm or greater than 8 mm.
4. Individual has the presence of FMD (defined as visible beading of the artery on angiography).
5. Individual has >50% stenosis in any treatable vessel.
6. Individual has a renal artery stent placed <3 months prior to the denervation procedure.
7. Individual has presence of a renal artery aneurysm defined as any localized increase in the diameter of the vessel.
8. Individual has disease not allowing any treatment in the main renal artery.
9. Individual has an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m2, using the 4 variable MDRD calculation (in mL/min per 1.73 m2 = 175 x SerumCr-1.154 x age-0.203 x 1.212 (if patient is black) x 0.742 (if female)).
10. Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%. (If the glycosylated hemoglobin in the patient's records is >3 months old (from the date of Screening Visit 2), or history of uncontrolled blood sugars raises concern, it is required to analyze glycosylated hemoglobin as part of Screening Visit 2 labs.)
11. Individual is taking SGLT2 inhibitor or GLP-1 agonists that have been prescribed <90 days prior to SV1 or who does not plan on remaining on these drugs for the duration of the trial.
12. Individual has had ≥1 episode(s) of orthostatic hypotension not related to medication changes within the past year or has a reduction of SBP ≥20 mmHg or DBP ≥10 mmHg within 3 minutes of standing coupled with symptoms during the screening process (at SV2).
13. Individual requires chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea (e.g. CPAP, BiPAP).
14. Individual with a history of narcotic drug abuse, is currently on methadone, or who has used narcotic drugs more than once in the month prior to Screening Visit 1.
15. Individual had documented primary pulmonary hypertension.
16. Individual has untreated secondary cause of hypertension (either known or suspected) or is taking drugs that increase sympathetic tone that could contribute to hypertension.
17. Individual has frequent intermittent or chronic pain that results in treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for two or more days per week over the month prior to Screening Visit 2.

18. Individual with HIV on anti-retroviral drug therapy without documentation that hypertension preceded initiation of anti-retroviral drug treatment.
19. Individual has a scheduled or planned surgery that, in the opinion of the Investigator, may affect study endpoints.
20. Individual has a documented condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the protocol-specified automatic/office blood pressure monitor (e.g., upper arm circumference outside cuff size ranges available by geography or arrhythmia such as atrial fibrillation that interferes with automatic monitor's pulse sensing and prohibits an accurate measurement).
21. Individual works night shifts.
22. Individual has severe cardiac valve stenosis for which, in the opinion of the investigator, a significant reduction of blood pressure is contraindicated.
23. Individual has a documented confounding medical condition, which in the opinion of the investigator, may adversely affect the safety of the participant (e.g. patients with clinically significant peripheral vascular disease, aortic aneurysm, bleeding disorders such as thrombocytopenia, hemophilia, or significant anemia).
24. Individual is pregnant, nursing or planning to become pregnant during the course of the study follow-up. (Note: Pre-menopausal female participants must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test prior to angiography).
25. Individual has a known unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable, in the opinion of the investigator, to comply with study follow-up requirements.
26. Individual is currently enrolled in a concurrent investigational drug or device study, unless approved by the study sponsor. (Note: For the purpose of this protocol, participants involved in extended follow-up studies for products that were investigational but are currently commercially available are not considered enrolled in an investigational study).
27. Individual is currently taking anti-mineralocorticoid drugs. (Note: Subjects may be enrolled as long as anti-mineralocorticoid drugs are weaned off at least 8 weeks prior to Screening Visit 1).
28. Individual has an active peptic ulcer or gastrointestinal (GI) bleeding within the prior six months from consent.
29. Individual has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions.
30. Individual has polycystic kidney disease, unilateral kidney, atrophic kidney, or history of renal transplant.

8.5. Subject Consent

All subjects must complete a Patient Information and Informed Consent form **prior** to undergoing any study-related procedures. Sites must comply with local regulatory requirements (latest version of ISO14155) and local EC/IRB policies for obtaining informed consent. The consent form will be provided under separate cover.

In advance of the consent discussion, the subject should receive the EC/IRB and Medtronic-approved Subject Informed Consent Form. During the consent discussion, the investigator or his/her designee (only in geographies where allowed) must fully inform the subject of all pertinent aspects and risks of the study. All items discussed in the Subject Informed Consent Form must be explained by research site staff designated on the Delegation Task List. The language used shall be as non-technical as possible and must be understandable. In the event the subject cannot read and/or write, the consent process shall be obtained by reading the consent form aloud to the prospective subject and the impartial witness, where applicable. Subject Informed Consent Forms should be made available in subject's native language.

Neither the investigator nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights. The subject will be provided ample time to read and understand the Subject Informed Consent Form and to consider participation in the study.

When the subject decides to participate in the clinical study, the site's current EC/IRB and Medtronic-approved Subject Informed Consent Form must be signed and personally dated by the subject and investigator or designee. If the subject is not able to read and/or write, an impartial witness shall also sign and personally date the consent form to attest that the information in the Subject Informed Consent Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

After all required parties have signed and dated the Patient Informed Consent Form, the investigator/or designee must provide the subject with a copy of the signed and dated Patient Informed Consent Form. The consent process should be documented in the subject's medical record.

The subject will be informed about the rights to "withdraw from the study at any time", "withdraw without any disadvantage and without having to provide reason."

8.5.1. Revisions in the Patient Information and Informed Consent form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's continued participation in the study. The investigator or designee should inform the subject in a timely manner.

Medtronic will revise the written the Patient Information and Informed Consent form whenever new information becomes available that may be relevant to the subject's continued participation in the study. The revised information will be sent to the investigator for approval by the EC/IRB and Competent Authority (CA), if required. After approval by the EC/IRB, a copy of this information must be provided to the participating subjects, and the information process as described above, in **Section 8.5** Subject Consent, needs to be repeated.

9. Study Procedures

The below section describes the study procedures that the subject will undergo during the clinical study.

9.1. Schedule of Events

9.1.1. Screening Visit 1

After confirmation that the investigator (or authorized delegate) and subject have personally signed and dated Patient Information and Informed Consent Form, the following assessments will be performed at the Screening Visit:

a) **Medical history** will be documented from the study subject to evaluate for prior or existing medical conditions and/or procedures that would exclude subjects from participation in the study.

b) **Office blood pressure** measurements will be obtained in accordance with study guidelines in **Appendix 16.5**. This blood pressure measurement will not be used as the baseline BP measurement but will be used, in conjunction with the subject's medical history, to determine if, in the investigator's judgment, the subject's BP at Screening Visit 2 will qualify for inclusion in the study following the antihypertensive drug washout period. However, if the subject's SBP is ≥ 180 mmHg, the subject will be excluded at Screening Visit 1. Subjects with an office SBP <180 mmHg and drug naïve subjects with an office DBP ≥ 90 mmHg are eligible to continue to the next study visit. Subjects with office SBP ≥ 180 mmHg and drug naïve subjects with an office DBP < 90 mmHg will be exited from the trial.

c) **Medication & adverse event reviews** will be completed to document baseline medication use and adverse events that occur after enrollment.

Subjects determined to not be eligible for procedure will be exited from the study, as described in the *Subject Exit from Study (***section 9.5.1**) of this CIP.

Notification to the primary physician caring for the subject of the subject's participation in the study will be made prior to the next screening visit. The letter should include a brief description of the study, indicate that the subject has given permission for the communication, and provide notification that medications that affect blood pressure should not be changed without consulting the principal investigator (or delegate) from the time of enrollment until after the 6-month follow-up visit as this would impact the major endpoint of the study.

9.1.2. Medication Washout Period

Following completion of Screening Visit 1, subjects on antihypertensive medication must be titrated off all antihypertensive medications over a three to four week washout period in a manner specified by the investigator. Subjects with an office systolic blood pressure of <180 mmHg after the minimum three week washout period (maximum four weeks) will continue to Screening Visit 2 (SV2). Subjects with an office systolic blood pressure of ≥180 mmHg at any point during and after the washout until procedure will be considered screen failures and will be exited from the study, as described in the *Subject Exit from Study* **section 9.5.1**.

9.1.3. Tw o Week Screening Visit

The purpose of this visit is to assess the subject's office blood pressure two weeks after the antihypertensive medication washout period has been started. Drug-naïve subjects do not need this visit. The target date is two weeks from Screening Visit 1 ±3 days.

a) **Clinical assessment** will be conducted to further evaluate for prior or existing medical conditions that would exclude subjects from participation in the study and to establish the subject's baseline medical condition. An individual experienced in performing histories and physical exams is required to assess subjects for safety assessment during the period of time that study subjects are not on antihypertensive medications.

b) **Office blood pressure measurements** will be obtained in accordance with **Appendix 16.5**. This blood pressure measurement will not be used as the baseline BP measurement but will be used, in conjunction with the subject's medical history, to determine if, in the investigator's judgment, the subject's BP at Screening Visit 2 will qualify for inclusion in the study following the antihypertensive drug washout period. If the systolic OBP ≥180 mmHg, the subject must be exited from the trial. A subject who is drug naïve but still has a two week screening visit conducted, should be considered a screen failure if their office diastolic blood pressure is <90 mmHg when the subject is drug naïve at SV1 through the 2 Week Screening Visit.

c) **Adverse event reviews** will be completed to document adverse events that occur after enrollment.

9.1.4. Screening Visit 2

Screening Visit 2 must occur within three to four weeks of completion of SV1. The following assessments will be performed at Screening Visit 2:

a) **Clinical assessment** will be conducted to further evaluate for prior or existing medical conditions that would exclude subjects from participation in the study and to establish the subject's baseline medical condition. An individual experienced in performing histories and

physical exams is required to assess subjects for safety assessment during the period of time that study subjects are not on antihypertensive medications.

b) **Office blood pressure measurements** will be obtained in accordance with **Appendix 16.5**. The average office blood pressure value will be used as the baseline value for comparison with follow-up visit office blood pressure values. Subjects with an office systolic blood pressure ≥150 and <180 mmHg and an office DBP ≥90 mmHg are eligible to continue the screening process.

c) Laboratory tests:

- **Basic metabolic panel Chem-7 (blood):** serum-creatinine, sodium, potassium, blood urea nitrogen (BUN) or urea, bicarbonate, chloride, and glucose. Bicarbonate will not be measured for subjects enrolled in Europe.
- **eGFR** will be calculated from the serum-creatinine in the Chem-7 panel for eligibility criteria by using the 4 variable Modification of Diet in Renal Disease (MDRD) Formula ***Note:*** If eGFR ≥42 and <45 mL/min/1.73m² then subject can be retested after hydration with a single, repeat test within two weeks.
- **hCG pregnancy test in blood/urine** for female subjects who are not postmenopausal. (This may also be completed the day of the procedure).
- **Drug testing (urine/blood)** to ensure medications are no longer present in the subject's system. A urine sample will be collected, preferably using the subject's first morning urine. A blood sample will be collected at the time of the visit. Drug testing samples collected for subjects that screen fail after obtaining the sample, must not be sent to the core lab for analysis.
- **24-hour ABPM** will be applied at the conclusion of Screening Visit 2 to confirm subject's baseline blood pressure. This value will be utilized as the baseline value for calculating change in 24-hour ABPM at various time points post-procedure. Subjects with a 24-hour systolic ABPM of <140 or ≥170 mmHg after completion of the screening visit will be exited from the study. Subjects with a 24-hr systolic ABPM of ≥140 and <170 mmHg are eligible to continue to the procedure visit. A single repeat measurement is allowed in case of the following: 1.) a technical issue with the blood pressure monitor or failure to follow ABPM instructions, or 2.) if a valid number of readings is not obtained, or 3.) if the 24-hr systolic ABPM measured 135 - <140 mmHg or 170-175 mmHg. ABPM must be conducted according to the guidelines in **Appendix 16.5**. If ABPM is repeated office blood pressure and drug testing must be repeated on day the ABPM is applied.
- **Adverse event reviews** will be completed to document adverse events that occur after enrollment.

Subjects determined to not be eligible for renal angiogram will be exited from the study, as described in the **Subject Exit from Study section 9.5.1** of this CIP.

It is expected that subjects who are eligible to continue to the renal angiogram will be scheduled for a procedure date within 14 calendar days of completion of Screening Visit 2. Completion of Screening Visit 2 is defined as the day the 24-hour ABPM is completed or date of lab results, whichever is later. No subjects will be eligible for the renal angiogram more than two weeks following Screening Visit 2.

9.1.5. Procedure Visit

9.1.5.1. Renal Angiography

The denervation procedure will occur once all eligibility criteria have been met as evaluated at Screening Visit 2 and during the renal angiogram.

Prior to undergoing renal denervation, the key inclusion/exclusion criteria will be re-confirmed by a renal angiography to ensure that subjects still meet previously assessed eligibility criteria. When scheduled, subjects will be prepared for a renal angiography according to standard procedures. For subjects with chronic kidney disease and/or other risk factors for contrast-induced nephropathy (CIN), the hospital's standard-of-care protocol for CIN prevention will be used. Prior to this procedure, appropriate systemic anticoagulation according to IFU requirements (e.g., ACT ≥ 250 sec). Hospital protocol driven or physician discretion driven use of short acting antihypertensive medications are permitted to control hypertension in order to mitigate bleeding from the arterial access site during the periprocedural period.

An aortogram and selective renal angiography will be performed with all subjects to confirm eligible renal artery anatomy. Ensure subject received a minimum aspirin dose of 250 mg intravenous or up to 325 mg oral (per local drug dose labelling) prior to procedure (unless subject is already taking aspirin on regular basis). If the subject is already taking aspirin daily then at least the usual daily dose should be given on the day of the procedure. If the subject has a documented allergy to aspirin, 75 mg per day of clopidogrel can be substituted; under these circumstances, a loading dose of at least 150 mg clopidogrel may be administered prior to the procedure per physician discretion.

9.1.5.2. Denervation Procedure

The renal artery denervation procedure will be performed according to the supplied Symplicity Spyral catheter *IFU*, Symplicity G3 generator *User Manual* and associated training provided by Medtronic. Pre-treatment with both anxiolytic medications and analgesic medications, such as morphine sulfate or fentanyl (with additional doses timed with ablation treatments as appropriate) should be considered. Blood pressure, O_2 saturation, and heart rate should be closely monitored both during the procedure and throughout the recovery phase from the conscious sedation administered.

The goal of the denervation procedure in this protocol is to ablate renal nerves where they are in close proximity to the vessel lumen by delivering RF energy in a helical pattern in the distal main renal artery and branch vessels coming off the main renal artery (first order branches).

The following are required:

- Placement of the catheter in each accessible renal artery branch vessel coming off the main renal artery to achieve ≤ 4 lesions in a helical pattern

  and

- Placement of the catheter in the most distal, treatable portion of the main renal and/or renal accessory arteries to achieve ≤ 4 lesions in a helical pattern

Note 1: Initial placement of the Symplicity Spyral catheter should not extend into the renal parenchyma as identified on fluoroscopic imaging.

Note 2: Depending on anatomy, branch and main renal artery should be treated with the goal of applying 4 ablations in each location.

Note 3: Uncommon subject anatomy variations may be treated per investigators discretion in accordance with protocol guidelines and procedural training.

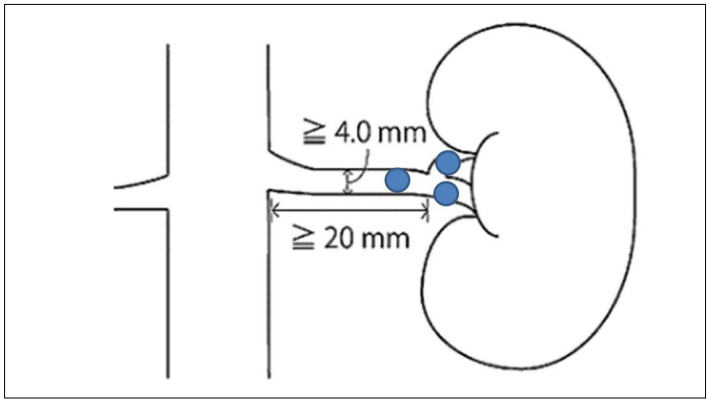

Figure 7: Schematic representation of positioning of Symplicity Spyral catheter.

Blue dots represent the required placement of the Symplicity Spyral catheter in eligible arteries for an example anatomy. More information and training will be provided as part of the procedural training.

Upon completion of the denervation procedure either manual compression or commercialized closure devices can be used to achieve hemostasis at the puncture site. As per usual clinical practice, consider use of short acting anti-hypertensive medications for blood pressure control in the cath lab and prior to removing arterial access. Strict adherence to anticoagulation parameters prior to sheath withdrawal following either hospital protocol or standard of care practices are strongly recommended.

9.1.5.3. Post-procedure data collection requirements

A copy of the renal angiogram cine procedure will be submitted to the angiographic core laboratory. Sedation type, procedure information, fluoroscopy time and contrast dye amount will be collected.

Symplicity G3 generator data will be downloaded by and submitted to Medtronic.

9.1.5.4. Post-procedure care

All subjects will be hospitalized overnight following the renal angiogram and procedure and standard-of-care post-intervention monitoring procedures will be followed.

Prior to discharge, the research staff will collect blood samples, assess for adverse events, and review study requirements with the subject to help ensure compliance with the follow-up schedule. An office blood pressure will also be obtained by study personnel. Various contact details (including telephone numbers and email address) should be obtained from the participant (not supplied to the sponsor) to ensure the ability to contact the subject at the required follow-up times (e.g., home, work, cell, and primary physician).

Subjects shall be prescribed a minimum of 75 mg aspirin for one month post-procedure. If the subject has a documented allergy to aspirin, at least 75 mg clopidogrel per day for one month post-procedure may be prescribed.

9.1.6. Follow -up Visits

See Table 3 for details on follow-up visit window and modality requirements for follow-up visits. See **Table 4** and **section 9.1.9** for escape subject requirements. Subjects will return for follow-up visits at 2 weeks, 1 month, 6 weeks, 8 weeks (non-escape only), 10 weeks, 3 months, 6 months, and 12 months post-procedure. Additionally, a 1 month and 4 month post-procedure in-office follow up is required for subjects with a systolic OBP >140 at the 3-month follow-up visit (see **section 9.1.10**).

Follow-up procedures for subjects treated are listed below and must be performed through 12 months follow up for each subject unless otherwise specified. After completion of the study required follow ups, the subjects will return to receiving standard of care follow up.

- **Clinical assessment** will be conducted at the 2 week, 1 and 3-months post-procedure follow-up visit to evaluate the subject's current medical condition. At 4, 6, and 12-months follow up an abbreviated clinical assessment of weight only is required.
- **Office blood pressure** measurements will be obtained in accordance with guidelines in **Appendix 16.5** at all follow-up visits.

- **Laboratory tests** are required at 1, 3, 6, and 12-month follow-up visits:
  - **Basic metabolic panel Chem-7 (blood):** serum-creatinine, sodium, potassium, blood urea nitrogen (BUN) or urea, bicarbonate, chloride, and glucose. Bicarbonate will not be measured for subjects enrolled in Europe.
  - **eGFR** will be calculated from the serum-creatinine in the Chem-7 panel for eligibility criteria by using the 4 variable Modification of Diet in Renal Disease (MDRD) Formula.
- **Medication and adverse event reviews** will be completed at each follow-up visit to assess any changes in medication usage or medical condition**:**
  - Enrollment (consent) to 6-months follow up: all medications and all adverse events
  - After 6-months follow up to 12-months follow up: all medications and all serious adverse events
- **Renal artery imaging** will be performed at the 6-month follow-up visit to assess if a renal artery stenosis is suspected. A renal duplex ultrasound (DUS) will be obtained at 6-months follow up and submitted to the DUS Core Laboratory. If the DUS is determined to be nondiagnostic a repeat DUS, a MRA, CT or angiogram will be performed (repeat imaging is to be completed within 30 days after confirmation of non-diagnostic imaging). If evidence of a clinically significant stenosis is indicated by the DUS or MRA/CT Core Laboratory, an angiogram must be obtained and submitted to the angiographic core laboratory.
  - If renal imaging is not obtained at the 6-month follow-up visit due to extenuating circumstances, renal imaging is required at the next scheduled study visit.
- **24-hour ABPM** will be conducted at the 3, 6, and 12-month follow-up visits post-procedure according to the guidelines in **Appendix 16.5**. A repeat ABPM will be required in the event of technical issues, failure to follow ABPM guidelines or if the minimum required number of daytime and nighttime readings is not obtained. If ABPM is repeated office blood pressure and drug testing (for 3-month follow up only) must be repeated on day the ABPM is applied.
  - Initiate medication re-Introduction for subjects with systolic OBP ≥140 mmHg at 3-month follow-up visit. Starting at the 3-month follow up after clinical assessment and a valid ABPM are completed.
- **Mortality assessment** will be completed by the investigational site when a subject cannot be reached after each of the protocol required follow-up visits.
- **Drug testing** (urine/blood) to ensure medications are no longer present in the subject's system. A urine sample will be collected, preferably using the subject's first morning urine. A blood sample will be collected at the time of the visit. Drug testing samples collected for subjects that screen fail after obtaining the sample, must not be sent to the core lab for analysis.

Alternative methods of data collection may be necessary in the case of extenuating circumstances, such as a global pandemic, when subjects are prohibited from coming into the office for required assessments. For all assessments completed via alternative methods in these circumstances, sites are not required to enter a protocol deviation for missing, and/or alternative data collection. Data unable to be collected remotely or via an alternative method should be collected at the next possible in-person visit. In the event a subject is unable to return for an in-office follow-up visit, the alternative methods of obtaining follow-up assessments are listed below:

In-home visit by trained and delegated site personnel or designee, for example, home health care personnel. The following assessments may not be completed with an in-home visit:

- **Renal artery imaging:**
  - Make every effort to schedule in-person renal artery imaging as soon as possible.
  - When possible, the subjects may be referred to a local imaging center for assessment. Local imaging technicians would require study training and delegation prior to assessment.

Virtual visit, inclusive of video with study subject, or a phone visit.

The following assessments may **not** be completed with a virtual visit or a phone visit:

- **Clinical assessment**: limited review to be completed per physician discretion.
- **Laboratory tests:**
  - When possible, the subject should be referred to a local laboratory to collect samples. Laboratory kits to be provided to subjects in advance of the visit by study site.
- **Renal artery imaging:**
  - Make every effort to schedule in-person renal artery imaging as soon as possible.
  - When possible, the subjects could be referred to a local imaging center for assessment. Local imaging technicians would require study training and delegation prior to assessment.
- **Office blood pressure and ABPM** units to be provided to the subjects in advance of the visit by the study site. Measurements collected by the subject may be collected and designated as subject-reported in the CRF.
  - Witnessed pill intake prior to ABPM, if applicable.
  - Documentation of pill intake will be assessed virtually or as confirmed verbally by subject.

9.1.7. Unscheduled Follow-up Visits

If subject returns to the institution between the protocol-required screening or follow-up visits for one of the following reasons: evaluation of subject for safety reasons, repeat procedures (serum creatinine blood draw, repeat renal imaging, or ABPM), or re-consenting, the visit will be treated as an unscheduled visit. The reason for the unscheduled visit, as well as any assessment data will be recorded on the Unscheduled Follow-up CRF and AE data on the Unscheduled visit CRF (if applicable). If the subject returns for another reason, documentation is not required.

9.1.8. Confirmatory Blood Draw s to Assess Renal Function

Serum creatinine values will be assessed throughout the study. A second blood draw will be required to confirm a sustained change in renal function in the event of one of the following:

- >50% increase in serum creatinine from baseline (Screening Visit 2)
- eGFR <15 mL/min/1.73m^2 using the 4 variable MDRD calculation

The additional blood draw must be taken at least 21 days from the date of the event noted above and documented on an Unscheduled Follow-up CRF. In the event the second blood draw results in the same event (e.g., >50% increase in serum creatinine from baseline), an adverse event must be reported. If the event is a continuation of an already-identified sustained elevation that did not return to <50% of baseline value, another blood draw is not necessary.

9.1.9. Anti-hypertensive medication escape criteria

In the event a subject's office SBP ≥180 mmHg, or there is a safety concern, from discharge up to and including the 3-month visit, the subject will be seen a second time within 72 hours for a repeat office BP. If the subject's office SBP remains ≥180 mmHg, the subject will be put back on an antihypertensive medication regimen per the investigator's discretion. All efforts should be made to obtain an ABPM and Chem-7 panel, and urine and blood for antihypertensive drug testing, prior to the subject being put back on medications. If the subject already started medications, the subject and investigator should consider if it is safe to take the subject off medications for at least two weeks prior to the 3M visit in order to obtain the requirements at the 3-month visit to ensure endpoint data is collected. The subject will be exited from the off medications portion of the study and will be followed according to **Table 4**. If the subject's office SBP< 180 mmHg, the subject will continue to be followed per **Table 3**. At any time while the subject is not taking antihypertensive medications, either the subject or the investigator may restart antihypertensive medications if there is a safety concern and the subject will be followed according to **Table 4**. All blood pressures must be taken according to the guidelines in **Appendix 16.5** with the exception of needing to be completed by 10:30 am. Visits for monitoring the subject's BP for these purposes must be documented on the CRF.

9.1.10. Medication Re-Introduction for Subjects with 3M Systolic OBP ≥ 140 mm Hg

Upon completion of a valid ABPM at the 3-month follow-up visit, subjects with an office SBP<140 mmHg do not need to be followed up for study purposes until the 6-month follow-up visit. Subjects with an office SBP ≥ 140 mmHg will begin an antihypertensive medication regimen of one or more of the following classes individually or in a combination pill with dosing at the discretion of the study investigator:

- ACE/ARB
- Calcium Channel Blocker
- Thiazide-Type Diuretic

Subjects will return at 4 months (±7 days) to perform a clinical assessment and obtain an Office Blood Pressure according to the guidelines in **Appendix 16.5**.

- The investigator may utilize his or her discretion in modifying the antihypertensive regimen.
- Any modification to the anti-hypertensive medication regimen must be documented on the CRFs.

To provide the appropriate oversight for study subjects, the visit schedule between the required 4-month and 6-month visits may need to be adapted to account for a subject's clinical status, complexity of the medication regimen, and/or the subject's blood pressure. If additional changes to the anti-hypertensive medication regimen are made between 3 and up to 6 months post-procedure, complete an unscheduled follow-up visit, and obtain an OPB according to the guidelines in **Appendix 16.5**. In addition, all medication changes are to be documented on the CRF. All medication used should be commercially available in the respective geographies and compliant with local labeling.

Table 3: Schedule of Treatments and Assessments

	Screening			Procedure		Post-procedure follow up								
Required Assessments	**SV1**	**2Wk**	**SV2**	**Procedure**	**DC**	**2Wk**	**1M**	**6Wk**	**8Wk**	**10Wk**	**3M**	**4M[1]**	**6M**	**12M**
Mode (O- in office, P-phone)	O	O	O			O	O	P[2]	P[2]	P[2]	O	O	O	O
Window (M-month, Wk-week, d-days)	--	±3 d			--	±3 d	±7 d	±3 d	±7 d	±3 d	±14 d	±7 d	±14 d	±30 d
Medical history	X													
Clinical assessment		X	X			X	X				X	X[8]	X[8]	X[8]
Renal denervation procedure				X										
OBP per study guidelines	X	X	X		X	X	X	X[4]	X[4]	X[4]	X	X	X	X
24h ABPM per study guidelines			X								X		X	X
Witnessed pill intake[3]													X	X
Medications prescribed[1]											X[1]			
Blood tests (Chem7)[4]			X		X		X				X		X	X
Serum or urine pregnancy test			X											
Drug testing			X								X			
Renal artery imaging– angiogram				X										
Renal artery imaging-DUS[5]													X	
Mortality assessment[6]						X	X	X	X	X	X	X	X	X
Medication and event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]

1: 4M follow-up is only required if 3M systolic OBP≥140 mmHg, prescribe AH medications according to **section 9.1.9** if SBP ≥ 140 mmHg

2: If medically necessary, phone contact may be replaced with office visit. OBP (per **Appendix 16.5**) to be obtained for an office visit or following alternative methods of data collection as described in **section 9.1.6**.

3: Witnessed pill intake (if subject is taking AH medications), complete after OBP measurements

4: Bicarbonate will not be measured for subjects enrolled in Europe.

5: DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CT or angiogram to be used if DUS is nondiagnostic. Renal angiography must be used if repeat DUS/CTA/MRA is nondiagnostic or stenosis >60-70% is suspected. If renal imaging is not captured at the 6M follow-up visit due to extenuating circumstances, renal imaging is required at the next scheduled study visit.

6: Mortality assessment will be completed by the investigational site when a subject cannot be reached after each of the protocol required follow-up visits

7: SAE only review required at 12M visit

8: Clinical assessment of weight only 8: Clinical assessment of weight only

Table 4: **Schedule of testing through 12 months for subjects with office SBP ≥180 mmHg (confirmed via 2 sets of measurements) or escape via investigator discretion during off-medication period post-procedure**

	Procedure		Post-Procedure						
Required Assessments	**Procedure**	**DC**	**2Wk**	**1M**	**6Wk**	**10Wk**	**3M**	**6M**	**12M**
Mode (O- in office, P-phone)			O	O	O	O	O	O	O
Window (M-month, Wk-week, d-days)	--	--	± 3 d	±7 d	± 3 d	± 3 d	± 14 d	± 14 d	± 30 d
OBP per study guidelines		X	X	X	X	X	X	X	X
Renal artery imaging[1]								X[1]	
Mortality assessment[2]			X	X	X	X	X	X	X
Medication and event review		X	X	X	X	X	X	X	X[3]

1: DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CT or angiogram to be used if DUS is nondiagnostic. Renal angiography must be used if repeat DUS/CTA/MRA is nondiagnostic or stenosis >60-70% is suspected. If renal imaging is not captured at the 6M follow-up visit due to extenuating circumstances, renal imaging is required at the next scheduled study visit.

2: Mortality assessment will be completed by the investigational site when a subject cannot be reached after each of the protocol required follow-up visits

3: SAE only review required at 12M visit

9.2. Assessment of Safety

Adverse event (AE) information will be collected by the site from subject enrollment (consent) through 6-months follow up. After the 6-month follow-up visit and until study termination only serious adverse events will be collected. AEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes, and the overall clinical outcome has been ascertained), or subject participation in the study has ended, or study termination.

The Investigator will report any adverse events that may occur to the sponsor, and will assess seriousness, relationship (to the device, procedure, and renal denervation therapy where applicable), subsequent intervention required, resolution status and whether the adverse event resulted in the subject's discontinuation from the study. The Investigator will provide further information regarding adverse events as requested by the sponsor.

9.3. Recording Data

9.3.1. Database/ Case Report Forms

Data collected on each subject will be recorded on a web-based CRF. This study will utilize an Oracle Clinical Remote Data Capture (RDC) system that is the property of Medtronic. Each enrolled subject is assigned a unique study ID number. Records of the subject/subject ID relationship will be maintained by the study site. Individual subject medical information obtained as a result of this study will be considered confidential.

Authorized site personnel as indicated on the Delegation Task List (DTL) will record the required data on CRFs. Study personnel delegated for CRF completion and/or approval per the DTL will be trained on the use of the RDC system and thereafter be provided with a username and password to access the system. Passwords are individual and cannot be shared.

The CRFs must be completed and updated to reflect the latest observations on the subjects participating in the study. The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each CRF. The Oracle Clinical RDC system maintains an audit trail of entries, changes, and corrections in CRFs. If a person only authorized to complete CRFs makes changes to an already signed CRF, the investigator shall re-approve this CRF.

The hospital files (electronic or paper) will constitute source data. For the purpose of adjudication of events by the CEC, relevant event-related source documents will be redacted and collected for events that need to be adjudicated by the CEC.

The CRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g., renal angiogram variables, procedural details) may vary from center to

center. The site may use technical worksheets if identified as source documents. Worksheets need to be signed and dated by the principal investigator or a delegated investigator.

The principal investigator is responsible for ensuring that all sections of each CRF are complete and correct and that those entries can be verified against source data.

Medtronic will be responsible for the processing and quality control of the data. Data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal SOPs and the Data Management Plan for this study. The study database will employ validation programs (e.g., range and logic checks) on entered data to identify possible data entry errors and to facilitate data validation.

9.3.2. Blood Pressure Monitors

The following equipment will be provided to the sites and utilized for assessing the endpoints of the study:

- Office blood pressure monitors
- 24-hour ambulatory blood pressure monitors

Medtronic will provide automated blood pressure monitors to participating centers for recording office based systolic and diastolic blood pressure through the course of the study. Blood pressure monitors will be provided to the sites for use with subjects to record ambulatory systolic and diastolic blood pressure at baseline and through subsequent follow ups. Medtronic will be responsible for the timely calibration of the monitors and replacement of monitors, in case of malfunction or failure to record accurate and reliable blood pressure data.

9.4. Deviation Handling

A study deviation is defined as an event where the investigator or site personnel did not conduct the study according to the CIP, EC/IRB, applicable laws or regulations, or the investigator agreement.

Regulations require that investigators maintain accurate, complete, and current records, including documentation of any deviations from the CIP including the date of and reason for the deviation. The deviations must be reported to the sponsor on the CRF.

Investigators are not allowed to deviate from the protocol, except under emergency circumstances to protect the rights, safety, and well-being of human subjects. Investigators are required whenever possible to obtain prior approval from the Medtronic Clinical Research Department before initiating changes in or deviations from the CIP, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in the study files. Prior approval is not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g., subject did not attend scheduled follow-up visit, blood sample lost by laboratory), however, the event, is still considered a deviation.

Deviations shall be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Deviations to protect the life or physical wellbeing of the subject in an emergency must be reported to Medtronic and the EC/IRB within five working days.

Subject-specific deviations will be reported on the Deviation CRF. Deviations that are not subject specific (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an investigator agreement) will be reported to Medtronic in writing. Investigators will also adhere to procedures for reporting study deviations to their EC/IRB in accordance with their EC/IRB requirements.

The investigational site's compliance with the CIP will be assessed on an ongoing basis. Corrective and preventive action plans will be developed and implemented to secure compliance. In cases of serious non-compliance, the sponsor may decide to stop subject enrollment and site participation at an investigational site based on its assessment of repeated occurrences of significant non-compliance.

Examples of deviations include but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the Subject Informed Consent used
- Failure to obtain EC/IRB approval before the start of the study
- Treated subject did not meet inclusion/exclusion criteria
- Follow-up visit not done
- Adverse events not reported in the required time frame as required by regulation or as specified in CIP
- Source data permanently lost
- Enrollment of subjects during lapse of EC/IRB approval

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrollment or ultimately terminate the investigator's participation in the clinical study. The sponsor shall consider terminating or suspending the participation of a particular investigational center or investigator in in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

Medtronic will provide investigational site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigation site.

9.5. Reporting Requirements

9.5.1. Investigator Reporting Responsibilities

Report	Submitted to	Description
Adverse events	Sponsor, EC/IRB, and local Competent Authority, where applicable	Refer to **Section 11.2** for reporting requirements.
Progress report	Sponsor and EC/IRB	Provide if required by local law or EC/IRB. (ISO 14155).
Withdrawal of EC/IRB approval	Sponsor	Investigator will inform Medtronic as soon as possible in case EC/IRB approval is withdrawn. In the US, the investigator must report a withdrawal of the reviewing IRB within five working days of the IRB's withdrawal.
Final report	EC/IRB (all sites), sponsor (US sites)	A copy of the Final Clinical Study Report will be provided to the EC/IRB and submitted in accordance with the EC/IRB policies and procedures. In the US, the site's final report must be submitted to the sponsor and IRB within three months after termination or completion of the investigation or the investigator's part of the investigation.
Deviations from Investigational Plan		
Planned deviation	Sponsor, EC/IRB, regulatory authority, as applicable by local regulations	Prior approval from Medtronic must always be obtained from Medtronic. If the deviation affects scientific soundness of the clinical study or the rights, safety, or welfare of the subject and is not an emergency, prior approval must be obtained from the EC/IRB and Competent Authority as applicable.

Report	Submitted to	Description
Other deviations	Sponsor, EC/IRB, regulatory authority, if applicable	Deviations that are beyond the control of the investigator (such as subject who fails to return to follow-up visit) or deviations that do not affect the scientific soundness of the clinical study or the rights, safety, or welfare of the subject and are not an emergency, should be submitted as they are identified by the investigational site or Medtronic staff. For emergency deviations to protect the life or physical wellbeing of the subject in an emergency, these must be reported to Medtronic and the EC/IRB within five working days. If an investigator uses a device without obtaining subject consent, the investigator shall report such use within 5 working days after device use.

9.5.2. Sponsor Reporting Responsibilities

Report	Submit to	Description
Withdrawal of EC/IRB or RA approval	EC/IRB, Investigators, and regulatory authorities, where applicable	In case of withdrawal of EC/IRB approval Medtronic will suspend the clinical study as described below. In the US, notification within 5 working days.
Premature termination or suspension of study	EC/IRB, Investigators, and regulatory authorities, where applicable	Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to EC/IRB and regulatory authorities.
Progress report	IRB/EC and RAs	This will be submitted to the IRB/EC only if required by the IRB/EC. In the US, progress reports will be submitted per FDA requirements.

Report	Submit to	Description
Final report	Investigators, and regulatory authorities, where applicable	Medtronic will provide all investigators with a copy of the final clinical study report of the clinical study. EC/IRBs and regulatory authorities will be informed when required. • The investigator shall have the opportunity to review and comment on the final report. • If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). The coordinating investigator shall sign the report. If no coordinating investigator is appointed, then the signature of the principal investigator in each study site should be obtained.
Emergency deviations from CIP	Regulatory authorities, where applicable	If required, Medtronic will inform regulatory authorities as soon as possible about any emergency deviations that affect scientific soundness of the clinical study or the rights, safety, or welfare of the subject.
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155:2020) Study site specific study deviations will be submitted to investigators periodically.

9.6. Subject Withdrawal or Discontinuation

9.6.1. Subject Exit from Study

There are many scenarios in which a subject may exit the study. **Table 5** details how the data will be handled for each scenario.

It is the subject's right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled, and without jeopardizing their future medical care. The investigator may withdraw the subject at any time to protect the health, safety, or welfare of the subject. The subject's vital status should be recorded at the last point of contact (if outside a study-required visit). Every effort should be made to collect the status of any ongoing adverse events, at a minimum. The subject will not be considered lost to follow up during the course of this study.

All subjects will be encouraged to remain in the study through the last follow-up visit, including receipt of any results such as valid ABPM, labs, imaging, etc. Subjects who discontinue participation prematurely will be included in the analysis of results; but will not be replaced in the enrollment of total study subjects. If the subject discontinues participating in the study prior to completing the study requirements, the reason for withdrawal will be recorded in the subject's study records.

If withdrawal from the study is due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow the subject's status outside the clinical study.

Table 5: Scenarios for Subject Exit from Study

Scenario	Follow up Required
Subject enrolled (Patient Information and Informed Consent form signed), but the procedure is never attempted	None
Subject enrolled and exits the study early due to any of the following: - death - withdrawal	Through point of death, withdrawal, or last visit completed; consent to continue to allow data collection from their medical records is required
Subject enrolled, undergoes renal denervation and completes the study requirements	Through a minimum of 12 months follow up post-procedure up to a maximum of 5 years follow up post-procedure.

9.6.2. Missed Follow -up Visits

Every effort should be made to ensure subjects return to the investigational site for all protocol required follow-up visits. If the subject is unable to complete an in-office, in-home, virtual or phone visit, the Investigator (or designee) must document the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting as outlined in **section 9.4**. If a subject misses a follow-up visit, they will not be considered lost to follow up and all remaining follow-up visits will be scheduled per protocol. The Investigator should also make every effort to contact the subject within the visit window, to collect the subject's vital status as well as information related to potential adverse events.

At a minimum, four attempts must be made to contact the subject and documented in the subject's study records before a visit can become a missed visit:

- 3 telephone attempts to the subject's last known phone number, and if unsuccessful,
- 1 letter from the PI to the subject's last known address sent by courier with tracking information.

10. Risks and Benefits

10.1. Potential Risks

The inexorable progression from asymptomatic hypertension to evidence of end organ disease is well known. Both embolic and thrombotic stroke as well as both systolic and diastolic heart failure, and progressive renal dysfunction are known to be companions of chronic hypertension. Beyond contributing to renal failure, hypertension plagues the treatment of subjects with end stage renal disease treated with dialysis and transplant. In aggregate, reduction of blood pressure is linearly related to reduction of mortality in population studies[19,20], with large individual subject variability depending on the presence of additional cardiovascular risk factors, such as lipid abnormalities, diabetes, cigarette smoking, and antecedent heart disease. Despite the availability of numerous pharmaceuticals from many different pharmaceutical classes, subjects often fail to attain adequate blood pressure control. Additionally, pharmaceutical interventions that rely on numerous medications are plagued with drug interactions and side effects, which contribute to physician decisions to discontinue medications and subject decisions to not remain persistent or compliant with the prescribed drug strategies. The development of an effective alternative treatment of hypertension, which offers an adjunct to pharmaceutical care or an alternative to undesirable pharmaceutical complications, may prove to be of obvious value to subjects, physicians, and the health system.

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance.

The primary risks of the renal denervation procedure are similar to the risks of all diagnostic procedures requiring catheterization of the arteries of the body. The following are potential risks of the catheterization procedure (including renal angiogram) in accordance with the IFU:

- Death – a complication or deterioration of health ultimately leading to a subject's death.
- Cardiopulmonary arrest – cessation of blood circulation and/or respiration due to dysfunction of the heart and/or lungs.
- Heart rhythm disturbances – disruption of normal heart rate or rhythm, including bradycardia treated with atropine.
- Embolism – formation and dislodgement of a blood clot (thrombus) or dislodgement of cholesterol/plaque within the blood vessel, which travels downstream into small vessels, blocking blood flow and causing temporary or permanent damage to organs distal to blockage. Emboli are known to cause myocardial infarction, stroke or kidney damage, peripheral ischemia and may ultimately lead to incapacitation or death.
- Complications at catheter insertion site in the groin:
    - Pain – discomfort at the catheter insertion site that can range from mild to severe.

  - Hematoma/Bruising – a collection of blood in the tissue surrounding the catheter insertion site.
  - Pseudoaneurysm – a collection of blood in the tissue surrounding the catheter insertion site due to ongoing leaking of blood from a blood vessel.
  - AV fistula – an abnormal connection between an artery and a vein (*i.e.*, caused by needle insertion through the femoral artery and vein).
  - Infection – localized redness, heat swelling and pain at the catheter insertion site.
  - Significant bleeding – blood loss from the catheter insertion site requiring surgery or transfusion of 2 or more units of packed red blood cells (PRBCs).
- Retroperitoneal bleeding – bleeding into the retroperitoneal space.
- Vascular complications requiring surgery – damage to an artery (*e.g.,* femoral) or vein requiring surgical repair.
- Perforation of a blood vessel – unintended puncture through the wall of a blood vessel, such as a renal artery, requiring repair.
- Dissection of a blood vessel – a tear within the wall of a blood vessel, which allows blood to separate the wall layers.
- Hypotension – low blood pressure.
- Hypertension – high blood pressure.
- Nausea – a sensation of unease and discomfort in the upper stomach with an urge to vomit.
- Vomiting – forceful expulsion of stomach contents through the mouth and/or nose.
- Complications associated with the contrast agents – adverse effects of contrast agents used during the procedure (*e.g.*, allergic reaction or radiocontrast nephropathy).
- Complications associated with medications commonly utilized during the procedure – known risks of medications commonly used during the procedure (*e.g.*, narcotics, anxiolytics, other pain medications, anti-vasospasm agents).

There are additional risks that could possibly be associated with the denervation procedure/therapy. These potential risks have not yet been quantified, but may include:

- Pain – discomfort that can range from mild to severe that may occur peri- and/or post-procedure.
- Damage to one or both kidneys, loss of kidney function, and/or need to remove a kidney – perforation of kidney or an occlusion of blood flow to the kidney (*e.g.*, from stenosis or embolism) and/or reduction of glomerular filtration rate or need for nephrectomy. If severe enough, this could require dialysis.
- Renal artery aneurysm – localized weakening and ballooning of the renal artery from the interventional procedure or the delivery of RF energy.
- Renal artery stenosis - narrowing of the renal artery due to the interventional procedure or the delivery of RF energy.

- Arterial spasm or constriction – Acute or chronic narrowing of the renal artery lumen diameter at denervation locations due to arterial muscle contraction, local tissue contraction or local edema.
- Thermal injury to the vasculature or other structure from energy application - damage to an artery, vein, or other structure due to the delivery of energy.
- Hypertension – worsening high blood pressure.
- Hypotension – low blood pressure. BP reduction may occur too far and/or too quickly and may cause end organ hypoperfusion.
- Orthostatic hypotension – temporary reduction of blood pressure when going from lying to standing, coupled with symptoms (*e.g.,* dizziness, light headedness).
- Hematuria – blood in urine.
- Hemorrhage – significant blood loss.
- Proteinuria – elevated levels of protein in urine.
- Electrolyte disturbances – an imbalance of the electrolytes (sodium, potassium).
- Skin burn – damage to the skin caused by energy conduction via the ground pad used with the Symplicity renal denervation system

The risks associated with not having a controlled blood pressure during the first four months include:

- Angina (chest pain, pressure or squeezing)
- Myocardial infarction (improper blood flow to the heart)
- Pulmonary edema (fluid accumulation in the air spaces of the lungs)
- Heart failure
- Stroke (disturbance in the blood supply to the brain)
- Atrial fibrillation (abnormal heart rhythm)
- Death

There are additional risks that could possibly be associated with the tests and procedures performed for the clinical study. These potential risks are described below.

The risks associated with subjects being off their antihypertensive medications during the washout period through three months post-procedure include:

- Death
- Stroke
- MI
- Angina
- Heart Failure
- Atrial fibrillation

- Pulmonary Edema

There are risks related to the blood tests required for the study, (e.g., excessive bleeding, fainting or light-headedness, hematoma (bruising), infection, or the requirement of multiple punctures to locate a vein to draw the sample).

This study involves exposure to a small amount of radiation. As part of everyday living, people are exposed to naturally occurring background radiation and receive a dose of about 3 millisieverts (mSv) each year. The effective dose from the denervation procedure is less than 5.5 mSv. The dose from this procedure is comparable to that received from many diagnostic medical x-ray and nuclear medicine procedures.

Subjects may undergo additional renal imaging via computerized tomographic angiography (CTA). The risks of undergoing a CT scan include ionizing radiation and contrast-induced neuropathy.

There is a possibility of risks to an unborn child. These risks are unknown. Women who are pregnant, nursing or expect to become pregnant during the course of the study are excluded from participating.

The study may involve unknown or unforeseen side effects or complications other than those mentioned above. If the above complications occur, they may lead to repeat or prolonged hospitalization, repeat procedures, emergency surgery, other emergency procedures, or, in rare cases, death.

The risks must be continuously monitored, assessed, and documented by the investigator.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are specifically defined in the CIP plan and constantly monitored.

10.2. Potential Benefits

Although no assurances or guarantees can be made, there is a reasonable expectation that the renal denervation procedure may be beneficial to the subject. Treatment with the Medtronic Symplicity Spyral multi-electrode renal denervation catheter and the Symplicity G3 renal denervation RF generator may reduce the nerve activity to and from the kidneys and cause a reduction in blood pressure. Evidence in the literature suggests that reduction of efferent sympathetic nerve activity to the kidney can a) cause relief of renal vasoconstriction, resulting in improved kidney function; b) reduce sodium retention, which can improve the clinical condition of subjects with medical problems related to excess salt and water; and c) reduce the release of renin - a renal produced hormone which is often elevated in subjects with either severe hypertension or heart failure.[21] Interference of afferent nerve activity from the kidneys can reduce central sympathetic activity, also causing reduction of blood pressure.

A reduction in blood pressure may result in the decrease or elimination of any symptoms associated with high blood pressure and/or reduction of blood pressure medications and the side effects related to medications. In addition, reduction in blood pressure may decrease the risk of other related adverse events associated with high blood pressure (risk of stroke, heart attack, renal failure, etc.).

Hyperactive sympathetic nervous system activity is associated with increased risk of death in subjects with heart failure.[22-26] With a reduction in renal sympathetic nervous system activity, the combination of reduced intra and extra renal neurohormonal activity may either retard the progression of ventricular hypertrophy or induce regression of hypertrophy - both of which could ameliorate symptoms associated with heart failure.[27]

Reduction of central sympathetic activity may also reduce resistance to the action of insulin – potentially improving glycemic control.[28,29]

10.3. Risk-Benefit Rationale

Residual risks of the Symplicity renal denervation system have been characterized as acceptable per Medtronic standard operating procedures for risk management. No further risk mitigation is required at this time. Medtronic will continue to evaluate the risk/benefit profile, safety, and performance of the product as data becomes available.

The following measures will also be taken to minimize risk to participants as part of this CIP:

- Physicians and staff will receive appropriate training prior to using the study devices. Training will include instruction on equipment and lab setup, assessing renal anatomy, intra-procedural subject management and monitoring, Symplicity Spyral catheter delivery and RF ablation, and post-procedural care.
- *Instructions for Use* are provided with each Symplicity Spyral catheter and a *User's Manual* is provided with each Symplicity G3 generator to ensure consistent use of the device within pre-tested parameters.
- The system's design and software include several safety mechanisms to reduce risk to the subject (limitations on temperature, time, impedance, and power delivered to the subject).
- Subjects will be closely monitored by appropriately trained personnel during the procedure and at regularly scheduled intervals for the duration of the study.
- Physicians will employ usual and customary clinical technique (e.g., sterile technique during catheter use and aseptic wound care procedures).
- A Data Safety Monitoring Board (DSMB) will be established to monitor the health, safety, and welfare of subjects and provide safety surveillance. The DSMB will review safety and efficacy data at pre-specified time points and provide recommendations regarding the continuation of the study to the sponsor.

The detrimental effects of uncontrolled hypertension are well established and an alternative treatment is worth investigation. Renal denervation using the Symplicity Spyral renal denervation system is one such alternative. Although there are several theoretical risks that could be associated with the device and procedure, the likelihood of those risks is believed to be low and will be carefully monitored in the study. The potential benefits, including blood pressure reduction and the associated effects of lowered blood pressure, justify the investigation of renal denervation in this study.

The Symplicity renal denervation system is considered a significant risk (SR) 2*1 CFR 812.*

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

For each reported adverse event, the Investigator will assess the events in terms of relationship to the device, relationship to the procedure and relationship to the renal denervation therapy (if applicable) as defined below:

- **Device:** A device related AE is defined as any AE for which a causal relationship between the event and the Symplicity Spyral catheter or Symplicity G3 generator can be established.
- **Procedure:** A procedure related AE is defined as any AE occurring within seven days post-procedure associated with the renal angiogram and intervention techniques involved in preparing for the actual renal denervation treatment.
- **Therapy:** A therapy related AE is a defined as any AE associated with a subject's physiological response to the renal denervation procedure.

For the purposes of the clinical report, Medtronic will classify each adverse event according to International Organization of Standardization (ISO) ISO 14155:2020.

Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system. This does not apply to the OBP or ABPM devices used within the study.

Adverse Event (AE): *(ISO14155 3.2)*

> Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.
>
> *NOTE 1: This definition includes events related to the investigational medical device or the comparator.*
>
> *NOTE 2: This definition includes events related to the procedures involved.*
>
> *NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.*

Adverse Device Effect (ADE): *(ISO14155 3.1)*

> Adverse event related to the use of an investigational medical device
>
> *NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.*

NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.

NOTE 3: this included 'comparator' if the comparator is a medical device.

Device Deficiency (DD): *(ISO14155 3.19)*

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling.

NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator. ***Potential for SADE*** *is defined as device deficiencies that did not lead to an adverse event but could have led to a SADE (ISO14155 7.4.3)*

a) if either suitable action had not been taken,

b) if intervention had not been made, or

c) if circumstances had been less fortunate

Malfunction: (*21 CFR 803.3(m*))

The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. Product labels, Instructions for Use, and User Manuals for this study are provided separately.

Product Complaint:

Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device that has been placed on the market.

- Abuse: abnormal use
- Misuse: user error

Serious Adverse Event (SAE): *(ISO 14155 3.45)*

Adverse event that led to any of the following

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, including chronic diseases or
3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): *(ISO 14155 3.44)*

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Health Consequences: *(21 CFR 814)*

Any significant adverse experience, including those which may be either life-threatening or involve permanent or long-term injuries, but excluding injuries that are non-life-threatening and that are temporary and reasonably reversible.

Serious Health Threat: *(ISO 14155 3.46)*

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users, or other persons, and that requires prompt remedial action for other subjects, users, or other persons

NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

As this study will be conducted in compliance to US Code of Federal Regulations (CFR) 21 CFR Part 812 the following definitions will apply:

Unanticipated Adverse Device Effect (UADE): *(21 CFR 812.3)*

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 clinical investigation plan or application (or a supplementary plan or application), or any other unanticipated problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.2. Reporting of Adverse Events and Device Deficiencies

Adverse event (AE) information will be collected by the site from subject enrollment (consent) through study termination or study exit (AEs up to 6-months follow up, SAEs up to 12-months follow up). AEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained), subject exit or study termination.

The Investigator will report any adverse events that occur to the sponsor, will indicate the date of the adverse event, and will assess seriousness, relationship (to the device, procedure, and renal denervation therapy where applicable), subsequent treatment or intervention required, resolution status and whether the adverse event resulted in the subject's discontinuation from the study. The Investigator will provide further information regarding adverse events as requested by the sponsor. In the event of an unexpected death, an autopsy should be requested.

Investigator reporting requirements of events and device deficiencies are outlined in **Table 6**.

Table 6: Required Timeframes for Adverse Event and Device Deficiency reporting from Investigator to Medtronic

Event Type	Timeframe for Reporting
Serious adverse event (SAE)	Immediately (but no later than 10 calendar days) after the investigator first learns of the event or of new information in relation with an already reported event.
Serious adverse device effect (SADE)	
Adverse device effect (ADE) or device related adverse event	
Unanticipated adverse device effect (UADE)	
All other adverse events (AE)	
Device deficiencies with SADE potential	As soon as possible, but no later than 48 hours after the investigator first learns of the event.
All other device deficiencies	

Adverse Event Sponsor reporting requirements in EU/EEA

In the EU/EEA region, MDR Art. 80(2) should be followed. **Table 7** documents the events to be reported and the relevant timeframe.

Table 7: Sponsor Adverse Events Reporting Requirements to National Competent Authority in EU/EEA

Events to Report	Reporting Requirements and Timeframe
Preceding investigational procedure related SAE (occurred in the study under same CIP) – including updates.	Immediately, but no later than 7 calendar days after awareness

In addition, it is the responsibility of the investigator and the sponsor to abide by AE reporting requirements stipulated by local law and the study site's EC/IRB.

11.2.1. Reporting Process

All adverse events, regardless of relatedness or outcome, must be recorded and reported through the 6-month follow up. After the 6-month visit has been completed, only serious adverse events (SAEs) are required to be recorded and reported. Adverse events will be documented on the appropriate CRF, reported by the investigational site to Medtronic, and to the EC/IRB (if required) within the EC/IRB required timeframe and local and national regulations, as applicable. Adverse events shall be reported on the adverse event CRF, one CRF for each adverse event term. The site should make all effort to provide the information required on the Adverse Event CRF and all adverse events should be reported within the event reporting timeframe requirements (refer to **Section 1.1.1**). For adverse events that require immediate reporting, initial reporting will be done on the CRF by completing as much information as is available. The AE CRF must be "saved as Complete" in the remote data capture (RDC) system to ensure it is reported to Medtronic as soon as possible. For any changes in status of a previously reported adverse event or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form.

All adverse events and device deficiencies will be reviewed by the Medtronic Core Clinical Solutions Safety Department. This review will include the determination whether the adverse event meets regulatory reporting requirements. The sponsor will ensure timely adverse event/device deficiency reporting to meet global regulatory requirements. In case the adverse event/device deficiency is related to a Medtronic market released device used during the study, the Medtronic employee who first becomes aware will report this device related adverse event/device deficiency to the Medtronic Product Experience

Management (PXM) within 48 hour timeframe.. The Medtronic Product Experience Management (PXM) will ensure prompt review and appropriate reporting.

Table 8: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, procedure, therapy
	Sponsor	Device, procedure, therapy, outside standard of care CIP procedure
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, UADE (for all system or procedure related AEs), DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by investigator

11.2.2. Non-reportable and Unavoidable Adverse Events

The following events do not qualify as adverse events and do not need to be reported:

- Documented pre-existing conditions without a change in the nature or severity of the condition
- Pre-planned hospitalizations for device change out (e.g. CRT, ICD, IPG)
- Appropriate cardiac device therapies received as a result of pre-existing arrhythmias
- SBP below 100 mmHg without producing symptoms suggestive of hypotension
- Unavoidable adverse events (**Table 9**)

The following table indicates the unavoidable adverse events that do not need to be reported. However, onset of any events listed in **Table 9** after the specified timeframes should be reported as an AE.

Table 9: Unavoidable Adverse Events

Event Description	Time Frame (hours) from the Renal Denervation Procedure
Anesthesia related nausea/vomiting	24
Low grade fever (<100^{o}F or <37.8^{o}C)	48
Mild to moderate bruising/ecchymosis (at insertion site)	168
Sleep problems (insomnia)	72
Back pain related to laying on table	72
Elevated blood pressure	During the procedure

11.2.3. Unanticipated Adverse Device Effect

Medtronic will conduct an evaluation of the unanticipated adverse device effect (UADE) in accordance with 21 CFR 812.46(b) and shall report the results of such evaluation to US FDA and to all reviewing ethics committees and participating investigators within 10 working days after Medtronic first receives notice of the effect. Thereafter, Medtronic shall submit such additional reports concerning the effect as FDA requests. Events reported for this study from all geographies will be reviewed and assessed for UADE reporting to the FDA. Events deemed to be UADEs will be submitted per local reporting requirements

11.2.4. Device Deficiencies

All device deficiencies and malfunctions will be documented on the appropriate CRF, reported to Medtronic, and reported to the EC/IRB (if required) within the EC/IRB required timeframe and local and national regulations. Device deficiencies that did not lead to an adverse event should be reported on a device deficiency form, one for each device deficiency. Please refer to the device deficiency CRF for the information to be reported for each device deficiency that did not lead to an adverse event. The device deficiency CRF must be “saved as Complete” in the remote data capture (RDC) system to ensure it is reported to Medtronic as soon as possible.

Device deficiency reporting requirements do not apply to the OBP or ABPM devices used within the study and will not be collected for these devices.

11.2.5. Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable, and AEs related to any market-released device during the study must be reported. Refer to local regulations for reporting requirements.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse, or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the sponsor must be done according to the local standard operating procedures. Medtronic will notify the RAs (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a subject, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
    - Life-threatening illness or injury,
    - Permanent impairment of a body function or permanent damage to a body structure,
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

11.2.6. Emergency Contact

Investigators should contact their responsible Medtronic study representative if they have any questions regarding reportable AEs or device deficiencies. sponsor contact information (including name, title, address, and telephone number(s)) is subject to change and will be maintained in a document separate from the CIP and provided to sites.

For reportable AEs or device deficiencies that require immediate reporting (see **Table 6**), initial reporting shall be done by completing the appropriate CRF. If the CRF is not available, the reportable AE or device deficiency form in the Investigator Site File must be completed, signed, and dated by the principal investigator or his/her authorized designee(s), and submitted to the RS MC2 Safety Portfolio APV CRDN rs.mc2safetyportfolioapvcrdn@medtronic.com email box or to the responsible Medtronic study representative. In due time, the AE or device deficiency needs to be entered in the CRF as well.

12. Data Review Committees

12.1. Clinical Event Committee

The clinical event committee (CEC) is composed of multiple clinicians with pertinent expertise who are not participants in the study and who do not have any other real or potential conflicts of interest. The CEC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study. Criteria will be established for selected complications and clinical events. At the onset of the study, the CEC will establish explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. The CEC will meet regularly to review and adjudicate pre-defined clinical endpoint events. If needed, the adjudication committee will require collection of additional source documentation from the clinical centers. The procedures by which the CEC will operate will be documented in a separate charter.

12.2. Data Safety Monitoring Board

The primary responsibility of the data safety monitoring board (DSMB) is to monitor the health, safety, and welfare of subjects. The DSMB will be composed of physicians who have experience in clinical studies in hypertension and/or cardiovascular indications and one biostatistician with experience in analysis of clinical trials. The members of the DSMB will not be investigators in the study and will be independent of Medtronic. Medtronic personnel may attend the meetings to answer questions but will not have a vote in determining the committee's recommendations.

Prior to the first DSMB review, guidelines for the identification, and evaluation of significant safety findings and/or increased frequency of events that may impact the rights, safety, or welfare of subjects will be established. All materials, discussions, and proceedings of the DSMB are completely confidential. The proceedings of each DSMB meeting will be recorded in minutes. The DSMB Chairperson will be responsible for providing a written recommendation regarding study conduct (e.g. continue as planned, specify a modification, or termination) to Medtronic and the study principal investigators. Additional details on the DSMB process, meeting, and data review schedule, as well as reporting expectations will be provided in the DSMB Charter.

12.3. Study Coordinating Investigators

The study coordinating investigators' (CI) role will be to provide overall supervision of the study, advise in study design, provide feedback on current practice and to assist in communications with clinical investigational sites in partnership with Medtronic. The study CIs will meet periodically by teleconference or in person to monitor the progress of the study, including subject enrollment, clinical site progress, and protocol compliance. The study coordinating investigators will also be responsible for reviewing the final results and determining the methods of presentation and publication together with Medtronic.

13. Statistical Design and Methods

13.1. General Methods

Descriptive statistics of continuous outcomes will be presented and include sample size, mean, standard deviation, median, interquartile range, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented. Paired t-tests will be used to compare changes in continuous measures from baseline to follow up. All statistical analyses will be performed using SAS for Windows (version 9.2 or higher) or other widely accepted statistical or graphical software. Subject data listings and tabular or graphical presentations of results will be provided, as applicable. Additional details on the analysis will be provided separately in the statistical analysis plan (SAP) for this study.

In accordance with the US FDA guidance document "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" [8], additional analyses will be performed to assess the effect of the COVID-19 pandemic on the study outcomes as described in the statistical analysis plan.

13.2. Analysis Sets

13.2.1. Intention-To-Treat Population

All enrolled subjects are included in the intention-to-treat (ITT) population. Subjects who meet the anti-hypertensive medication escape criteria (OSBP≥180 mmHg or safety reasons) will be analyzed using last observation carried forward (LOCF) for their blood pressure measurements. More details on the algorithm can be found in the table specifications document. Safety outcomes, and office and ambulatory blood pressure outcomes out to three months will be presented for this population.

13.2.2. Modified Intention-To-Treat Population

All enrolled subjects except subjects who meet the anti-hypertensive medication escape criteria (OSBP≥180 mmHg or safety reasons) will be excluded from the modified ITT population. Office and ambulatory blood pressure outcomes out to three months will be presented for this population.

13.2.3. Per Protocol Population

All treated subjects, meeting the following criteria are included in the per protocol population analysis::

1. Subjects showing medication compliance in blood and/or urine (via drug testing data) at Screening Visit 2 (SV2) and three months post-procedure.

2. Exclude subjects with protocol deviation code 101 (consent not obtained).

3. Exclude subjects who do not meet the following inclusion/exclusion criteria:

   - Inclusion: Individual has an office systolic blood pressure (SBP) ≥150 mmHg and <180 mmHg and an office DBP ≥ 90 mmHg measured at Screening Visit 2, according to the guidelines in **Appendix 16.5** of the CIP.
   - Inclusion: Individual has a 24-hour ABPM average SBP ≥140 and <170 mmHg measured at Screening Visit 2, according to guidelines in **Appendix 16.5** of the study protocol.
   - Exclusion: Individual has undergone prior renal denervation.
   - Exclusion: Individual has renal artery anatomy that is ineligible for treatment.
   - Exclusion: Individual has one or more of the following conditions: stable or unstable angina within three months of enrollment, myocardial infarction within three months of enrollment; heart failure, cerebrovascular accident or transient ischemic attack, or atrial fibrillation at any time.

4. Exclude subjects meeting the anti-hypertensive medication escape criteria (OSBP >180 mmHg or safety reasons).

Office and ambulatory blood pressure outcomes out to three months will be presented for this population.

13.3. Sample Size Justification

This study does not have a statistically powered hypothesis to determine if renal denervation performed in the distal main renal arteries and first order branches is as effective as the procedural approach in the SPYRAL HTN-OFF MED clinical study. The sample size of 50 subjects was chosen to provide a reasonable estimate of the efficacy of this procedural approach. In the original first phase of the SPYRAL HTN-OFF MED, only 38 subjects were sufficient in demonstrating efficacy (ASBP drop of -5.5 mmHg, with 95% CI of -9.1 to -2.0 and significant p-value of 0.003). By enrolling 50 subjects in the current study, we allow for potential missing outcomes data.

13.4. Efficacy Endpoints – Propensity Score Adjustment

Because this is a single arm study, the efficacy endpoints at three months will be compared to the RDN treated subjects from the SPYRAL HTN-OFF MED clinical study using propensity score stratification (subclassification) adjustment. The following covariates will be considered for propensity score analysis: baseline BP, age, gender, BMI, and diabetes.

The treatment effect will be assessed within each propensity score stratum, and the strata-specific effects combined to yield an overall treatment effect (DYSTAL minus SPYRAL HTN-OFF MED RDN arm), together with a two-sided 95% confidence interval.

The ITT population defined in 13.2.1 will be the primary analysis population, and secondary analyses will be performed on the modified ITT and per protocol populations in 13.2.2 and 13.2.3.

Further details will be provided in the study SAP.

13.5. Safety Endpoint Analysis

All the safety endpoints will be adjudicated by the clinical events committee (CEC). The safety endpoints will be summarized using counts and percentages, and no comparison group will be used for the safety analysis.

These analyses will be performed for the ITT population defined in 13.2.1.

13.6. Analysis of Baseline Characteristics

All clinically relevant baseline variables will be tabulated and reported. Categorical variables will be reported using counts and percentages, and continuous variables will be reported by giving the number of known values, the mean, standard deviation, median, interquartile range, minimum and maximum values.

13.7. Missing Data

Every effort will be undertaken to minimize missing data. Unless otherwise specified, no statistical techniques will be used to impute missing data for continuous or categorical outcomes. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

14. Study Administration

14.1. Monitoring

Monitoring oversight will be provided by Medtronic and detailed in a Medtronic internal monitoring plan separate from this CIP.

Monitoring visits will be conducted during the course of the study in accordance with Medtronic SOPs and the monitoring plan. The site initiation visit (SIV) will be performed before the first subject is enrolled once it has been verified that the site is prepared for the study and the requirements for starting subject enrollment are met. Documentation of training of the site team will be collected during the SIV, as well as all required regulatory documentation such as curriculum vitae, delegated task listing, etc.

In order to ensure a high degree of data quality, periodic monitoring visits will be performed at recruiting clinical centers. Site monitoring will be conducted to monitor compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. Frequency and timing of monitoring visits shall be determined by the sponsor for each site based on enrollment rate and volume, study compliance and findings from previous visits.

The monitor will perform source data verification by reviewing subject documents according to the monitoring plan. After the 3-month follow-up visit through study closure, subject-level data will be monitored for adverse events and blood pressure data only. All Patient Information and Informed Consent forms will be checked for subjects undergoing the procedure. The monitor will perform review of key variables for all treated subjects (including but not limited to, inclusion/exclusion criteria, endpoints, and safety) on the CRFs against subject's source documents per the monitoring plan. In addition, all available source documentation will be reviewed for potential adverse events and device deficiencies. Any discrepancies will be noted and resolved. The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic study personnel during these monitoring visits. The site staff should be also available outside of monitoring visits by email or phone when questions arise regarding subject information. In the case the principal investigator is not available during the monitoring visit, a phone call follow up with the monitor can be performed to discuss the observations of the monitoring visit.

The monitor will confirm periodic testing, calibration and maintenance of equipment used for study assessments such as the automated office blood pressure and ambulatory blood pressure monitors according to local standard of practice. Furthermore, the calibration and maintenance of the Symplicity G3 generator that is to be conducted by Medtronic's technical support staff.

Monitoring activities will be documented in the monitoring visit follow-up letters to be sent to the principal investigator and include a summary of what the monitor reviewed and the observations

regarding the completion of previous action items, significant findings, facts, deviations, conclusions, and recommended actions to be taken to secure compliance.

The sponsor will provide updated contact lists to the investigational sites.

14.2. Data Management

All records and other information about subjects participating in this study will be treated as confidential. The investigator will mark clinical records to indicate that the subject is enrolled in this clinical investigation.

Medtronic will collect data and monitor study records. Auditors, EC/IRB members, inspectors (governmental regulatory authorities) may also have access to the study records. Participating subjects will not be identified by name in any published reports about this study.

14.2.1. Electronic Data Capture

Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection. All data will be stored in a secure, password-protected database. All users will be trained on the use of the database prior to obtaining access. Once access is granted, users will have a unique user ID and will create their own password. Data stored electronically shall be maintained in compliance with 21 CFR Part 11. The database for this study will be maintained according to corporate policy and record retention schedule.

The investigator must ensure accuracy, completeness and timeliness of the data reported in the CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed, and dated by the principal investigator, and filed in the subject medical file. Only authorized persons can complete CRFs. CRFs shall be signed by investigators (physicians only) as specified on the delegated tasks list included in the investigator site file.

The electronic data capture (EDC) system maintains an audit trail on entries, changes, or corrections in CRFs. Upon completion of a CRF the investigator shall sign the CRF in a timely manner, if a change to an already signed CRF occurs, the investigator shall re-sign this CRF.

Sites will be instructed to upload or transmit renal imaging media, source documents, raw 24-hour ABPM data, and other data required to be collected during the course of the study. The site should make every effort to de-identify personal subject information prior to transmission.

14.2.2. Source data on Case Report Forms

Data entered must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

CRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g., echocardiography variables) may vary from site to site; the site may use source document worksheets if identified as source documents and are signed and dated appropriately.

14.2.3. Time windows for completion and submission of Case Report Forms

CRFs are recommended to be entered into the RDC system within 10 working days of the completion of the protocol-specified follow-up visit or sooner as requested by the sponsor.

14.2.4. Data review and processing

Data management will be done according to Medtronic SOPs and the data management plan for this clinical study. These documents will be made available on request. All collected data will be reviewed for completeness, correctness, and consistency. In case of issues, queries will be sent to the investigator to complete, correct or comment on the data.

14.3. Direct Access to Source Data/Documents

14.3.1. Accessibility of investigational site staff and study materials

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the clinical study manager. This accessibility is of particular importance for reviewing data in the CRF. Direct access to subject medical files for source data verification will need to be granted and prepared for monitoring visits, audits and regulatory inspections.

14.3.2. Audits and investigation site inspections

Medtronic may conduct audits at participating investigational sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities, independently of the employees involved in the clinical study. Regulatory bodies may also perform inspections at participating

investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the clinical study manager.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study - related monitoring, audits, EC/IRB review, and regulatory inspections.

14.4. Confidentiality

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject ID number (SID) to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the site. A subject identification log will be maintained as part of the investigator site file. This log will serve as the link between the subject study ID and an individual subject. This log must remain at the study site at all times.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

Investigational sites will protect the personal information of subjects in accordance with national, local and EC/IRB requirements. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

14.5. Liability

14.5.1. Insurance

Medtronic, Inc. (including all wholly owned subsidiaries, including Medtronic Bakken Research Center (BRC) maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC/IRB.

14.5.2. Subject compensation and indemnification

Subjects may receive compensation for their participation in this study, according to local EC/IRB policies and procedures. Medtronic will provide subject indemnification according to local laws where this study

will be conducted and as outlined in the clinical trial agreement. Reimbursement of travel cost will be considered if allowed by local regulations.

14.6. Clinical Investigation Plan Amendments

All CIP amendments need to be approved by Medtronic, respective EC/IRB, and regulatory authorities. Medtronic is responsible for regulatory authority approval or notification of CIP updates or amendments if applicable according to local regulations. In Europe, the sponsor might be responsible for submission to the EC/IRB if allowed by local regulation. The investigator will only implement the amendment after approval of the EC/IRB, regulatory authority, and sponsor. Furthermore, investigators shall sign any approved amendment for agreement.

The investigator may propose any appropriate modification(s) of the CIP or investigational device/product or investigational device/product use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

14.7. Record Retention

14.7.1. Investigator Records

The investigator must retain the investigator site file, subject medical files and CRFs in accordance with local law and regulations for a minimum period of two years after study closure (or longer if local laws require) after study completion in the investigational site.

No study document or image will be destroyed without prior written agreement between the sponsor and the investigator. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials. The sponsor must be consulted if the investigator wishes to assign the files to someone else, move them to another location, or is unable to retain them for the specified period.

The sponsor will retain the study records according to Medtronic corporate policy and record retention schedule.

If Medtronic wishes to retain these records for a shorter or longer period than specified above, Medtronic will notify the investigational sites of the intent and consult with the institutions on the methods of discarding or moving records. In addition, Medtronic will inform the investigational sites of expiration of the retention period prior to when the retention period expires. Upon the completion or termination of the investigation, Medtronic will maintain study records under its responsibility and Medtronic policy.

At a minimum, the following records must be kept by the investigator:

- Medtronic and EC/IRB approved CIP and any amendments
- Investigator's Brochure (if applicable) and/or *Instructions for Use* and any amendments
- Medtronic and EC/IRB approved Patient Information and Informed Consent Form
- EC/IRB notification, correspondence, and approval
- EC/IRB voting list
- Any reports to EC/IRB and regulatory authority
- Source documentation
- Subject Identification log
- Normal values or ranges for lab tests
- Lab certificate
- Documentation for equipment maintenance and calibration
- Regulatory authority approval or notification and relevant correspondence
- Fully signed clinical investigation agreement and confidentiality agreement (if not included in the clinical investigation agreement)
- Financial disclosures from investigators
- Insurance certificates, if applicable
- Completed delegated task list and curriculum vitae of investigation site personnel
- Training documentation of all investigation site personnel
- Relevant communications
- Signed, dated, and fully executed Patient Information and Informed Consent form
- Fully executed CRFs and corrections
- Reports of adverse events and device deficiencies
- Device and drug accountability records
- List of investigational sites
- Statistician analysis and clinical investigation report (final report)
- Any other records that may be required by hospital regulations or local law

14.7.2. Sponsor Records

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study
- All approved versions of the CIP and any amendments
- All approved versions of the Investigator Brochure and/or *Instructions for Use* and any amendments
- Sample of labeling attached to the investigational device

- Curriculum vitae of investigators and investigational site personnel (as required by local law)
- Delegated task lists and training records of investigators and investigational site personnel
- List of investigational sites
- Names/contact information of monitors
- EC/IRB approvals/notifications and regulatory approvals/notifications
- EC/IRB voting list
- Normal values or ranges for lab test
- Documentation for equipment maintenance and calibration
- Lab certificate
- Any reports to EC/IRB and regulatory authority
- Statistical analysis and clinical investigation report (final report) EC/IRB approvals/notifications and regulatory approvals/notifications
- Signed clinical investigation agreements and signed agreements with third parties
- Insurance certificates
- Shipping records for investigational devices, drugs provided for purposes of the study, and clinical-investigation related documents and materials
- Sample of approved Patient Information and Informed Consent forms
- Site visit reports
- Adverse event and device deficiency reports
- Financial disclosure information
- Fully executed CRFs and corrections

14.7.3. Source Documents

Data entered on the CRF must be traceable to source documents. Source documentation is defined as the first time data appear, and may include original documents, data and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study). Information in source documents (i.e., medical history/physical condition) dated prior to the Patient Information and Informed Consent form signature date may be used to verify subject eligibility criteria.

Clinical records must be marked to indicate a subject has been enrolled into the clinical study.

The CRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records may vary from site to site; the site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the CRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records are provided as source documents, or where copies of source documents are retained as source documents, they should be signed and dated by a member of the investigational site team making a copy with a statement indicating they are a true reproduction of the original source document.

The source documents **must be made available** for monitoring or auditing by the sponsor's representative or representatives of the competent authorities and other applicable regulatory agencies.

Copies of pseudonymized source documents will be requested to support event adjudication by the clinical events committee.

14.8. Publication and Use of Information

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, EC/IRBs and CAs of participating countries when required by local law.
- Registering and posting the study results on a publicly accessible database, ClinicalTrials.gov based on the posting rules stipulated.
- Submitting for publication the primary study results after the study ends.
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences.
- Making an individual study sites study data accessible to the corresponding investigator after the completion of the study, if requested.

Medtronic may form a publications review committee. Member(s) of the publications review committee may include, but are not limited to, the study PIs, the Medtronic clinical study manager or publication manager, and other Medtronic personnel.

Participating investigators and members of the study PI's research teams may submit publication ideas through the publication committee and may author publications. The publications review committee is responsible for developing a publication plan overseeing the development of case reports, manuscripts, and abstracts, identifying and appointing the manuscript/abstract first author(s)/writer(s), and identifying Medtronic personnel responsible for assisting the first author. The publications review committee may refine the publication plan during the course of the study if needed.

At the conclusion of the study, a multi-center manuscript may be prepared for publication in a reputable scientific journal. The publication of the principal results from any single study center experience within

the study is not allowed until the preparation and publication of the multi-center results. Any follow-up publications would require prior written approval by publications review committee.

Authorship will be determined based on the International Committee of Medical Journal Editors (ICMJE) published guidelines and GPP2 (Good Publication Practice) guidelines and will include, at a minimum:

a. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
b. Drafting the article or revising it critically for important intellectual content
c. Final approval of the version to be published
d. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Final criteria for selecting first and subsequent authors will be determined and documented in the publication plan.

14.9. Suspension or Early Termination

Early termination of the study is discontinuance, by sponsor or by withdrawal of EC/IRB or local regulatory body approval, of an investigation before completion. This is possible for the whole study, for all centers in a country, or for a single center.

Study suspension is a temporary postponement of study activities related to enrollment and distribution of the investigational product(s). This is possible for the whole study, for all centers in a country or a single center. In the case of study suspension or early termination, it is up to the sponsor's discretion to assess whether or not to continue the clinical study at the respective investigational site(s).

14.9.1. Study-wide termination or suspension

Possible reasons for considering study suspension or termination of the study for all centers include but are not limited to:

- AEs and device deficiencies associated with the system or product under investigation which might endanger the safety or welfare of subjects
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (medically/ethically justifiable) where the study is operating under regulatory body authority

14.9.2. Investigator/ study site termination or suspension

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial EC/IRB approval or annual renewal of the study
- Consistent non-compliance to the CIP (e.g., failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow ups, etc.)
- Lack of enrollment
- Noncompliance to regulations and the terms of the clinical trial agreement (e.g., failure to submit data in a timely manner, failure to follow up on data queries and monitoring findings in a timely manner, etc.)
- EC/IRB suspension of the center
- Fraud or fraudulent misconduct (as defined by local law and regulations)
- Investigator request (e.g., no longer able to support the study)

14.9.3. Procedures for planned study closure, termination, or suspension

14.9.3.1. Medtronic-initiated

Medtronic will promptly inform the clinical investigators of the reasons for a study termination or suspension and inform the regulatory authority(ies) (where required per regulatory requirements).

- In the case of study termination or suspension for reasons other than a temporary EC/IRB approval lapse, the investigator will promptly inform the EC/IRB.
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow up is provided.
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic. Subjects already enrolled should continue to be followed out of consideration of their safety, rights, and welfare.

14.9.3.2. Investigator-initiated

The investigator will promptly inform:

- Medtronic and provide a detailed written explanation of the termination or suspension.
- The institution (where required per regulatory requirements).
- The EC/IRB.
- The subjects and may inform the personal physicians of the subjects to ensure appropriate care and follow up is provided.

In the case of a study suspension:

- Subject enrollment must stop until the suspension is lifted.
- Subjects already enrolled should continue to be followed out of consideration of their safety, rights, and welfare.

14.9.3.3. Ethics Committee/ Institutional Review Board initiated

The investigator will promptly inform:

- Medtronic and provide a detailed written explanation of the termination or suspension within five business days.
- The institution (where required per regulatory requirements).
- The subjects and may inform the personal physicians of the subjects, with the rationale for the study termination or suspension.

In the case of a study suspension:

- Subject enrollment must stop until the EC/IRB suspension is lifted.
- Subjects already enrolled should continue to be followed in accordance with EC/IRB policy or its determination that an overriding safety concern or ethical issue is involved.

14.10. Role of Sponsor Representatives

As the sponsor of this clinical study, Medtronic has the overall responsibility for the conduct of the study, including assurance that the study will be conducted according to international guidelines including latest version of ISO 14155 and local laws. In this study, Medtronic will have certain direct responsibilities and may delegate other responsibilities to consultants and/or contract research organizations.

The principles of the Declaration of Helsinki have all been implemented in this study by means of the Patient Information and Informed Consent process, EC/IRB approval, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

Medtronic's general duties consist of submitting applications and information to appropriate regulatory authorities, obtaining EC/IRB approvals prior to allowing shipment of devices, selecting qualified investigators, ensuring proper clinical site monitoring, ensuring subject informed consent is obtained and ensuring that the EC/IRB and relevant regulatory authorities are promptly notified of significant new information about the investigation.

Medtronic is responsible for providing quality data that satisfies regulations and informing investigators, EC/IRB, and relevant regulatory authorities of UADEs/SADEs and deviations from the investigational plan as appropriate. The Medtronic clinical study team will provide written progress reports and a final report.

Sponsor representatives may provide support at the study site as required for the study under supervision of the principal investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Technical support at RDN procedure under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites
- Monitoring and auditing activities
- In addition, for this study, sponsor representatives may be authorized by the principal investigator to perform the following significant study related duties:
  - Support study investigators in performing the study procedure
  - Support data collection during the procedure and device testing

Support data collection during the study follow-up visits.

14.11. Site Selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

An investigational site may be selected for participation in the clinical study if compliant with the following requirements:

- Investigator has previous experience with the Symplicity Spyral renal denervation system.
- Investigator should have adequate staff that is accessible and has time to manage the study.
- Investigator should have adequate staff to perform blood pressure measurements.
- Investigator, and sub-investigators (if applicable) and all key site staff must be willing to provide his/her curriculum vitae.
- Investigational site must be willing to comply with the CIP and data collection requirements, including timely reporting of adverse events and device deficiencies as required by the CIP.
- Investigational site has demonstrated experience with conducting clinical (device) studies that comply with applicable regulatory standards.

- Investigational site is willing to participate in follow-up of subjects for a minimum of 12 months (and up to a maximum of 5 years).
- Investigational site has an internet connection with sufficient speed of data transfer.
- Investigational site agrees to one RDN operator per site unless an exception is granted in writing by the sponsor.

A list of participating investigational sites and IRBs, including contact information, and investigators (with titles), will be available as a separate document.

14.12. Site Activation

Prior to investigational site activation or subsequent involvement in clinical study activities, Medtronic will provide clinical study training relevant to the involvement of personnel conducting clinical study activities. Medtronic will train site personnel on, but not limited to, the CIP, relevant standards and regulations, informed consent, written clinical investigation agreements, data collection and reporting tools, investigator responsibilities, as well as device/product training. Study specific training will be documented prior to investigational site activation.

Training will occur prior to site activation at each site, and will include at a minimum the following topics (as applicable to the role at the site):

- Technical overview of device(s)
- Procedural training for proceduralist
- CIP overview and study procedures
- Investigational device disposition and accountability procedures
- Procedures for returning unused/explanted devices
- CRF completion and management, including electronic data entry
- Investigator and sponsor responsibilities
- Procedures for obtaining informed consent
- EC/IRB requirements
- Adverse event/device deficiency reporting procedures and timelines
- Deviation reporting procedures
- Monitoring requirements and expectations
- Potential regulatory inspections and audits by the sponsor or sponsor representative
- Site record maintenance and retention
- Regulatory requirements for commercially approved devices in a clinical study, including timely adverse event and complaint reporting
- Any additional regulatory requirements

The sponsor will supply all required study materials for appropriate data collection before study start. Data collected on each subject will be recorded on a web-based electronic CRF. The passwords for the electronic CRF will only be distributed to investigational centers where the sponsor has written documentation of site readiness.

Investigational sites will receive a formal letter of site activation, upon receipt of or completion of the following:

- Curriculum vitae of the principal and sub-investigators and all key site staff
- A signed trial agreement.
- Financial disclosure from the investigators
- Competent Authority approval (as applicable to the geography)
- A copy of the EC/IRB approval letter, along with the voting roster
- The EC/IRB approved subject information and informed consent form
- Documented training (at least CIP, CRF, EDC, ICF process and product training (as applicable to their role)) of the investigative team
- Lab certificate and lab normal values/ranges
- Delegated task list
- Confirmation of calibration and maintenance of equipment and maintenance of facilities

- Confirmation of adequacy of equipment/facilities (e.g., a quiet room to perform the blood pressure measurements)

Medtronic will control the supply of study materials and will only grant site activation when above activation criteria are met, and the site receives a formal activation letter from Medtronic.

14.12.1. Curriculum Vitae

Prior to study start, a current signed and dated curriculum vitae from the principal investigator, all sub-investigators and all key site staff participating in this clinical study as listed on the delegated task list shall be obtained, evidencing the required qualifications, including the year, and where obtained, and including their current position at the investigational site. The signature on the CV must be dated within three years prior to the date of activation of the investigational site.

14.12.2. Clinical Trial Agreement

Medtronic contracts with participating institutions/investigators through a clinical trial agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic. A clinical trial agreement shall be in place, signed by the participating investigational site and/or principal investigator of each investigational site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the CIP and subsequent amendments, by a fully executed agreement. Amendments to the CIP shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

15. References

1. Mancia G, Grassi G, Giannattasio C, Seravalle G. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. Hypertension 1999;34:724-8.
2. Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. Mayo Clin Proc 2009;84:822-30.
3. Joles JA, Koomans HA. Causes and consequences of increased sympathetic activity in renal disease. Hypertension 2004;43:699-706.
4. Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. The Lancet 2009;373:1275-81.
5. Coruzzi P, Musiari L, Mossini GL, Ceriati R, Mutti A. The renin-aldosterone system and renal function in kidney transplantation. Clinical nephrology 1994;41:225-9.
6. Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. The Lancet 2017;390:2160-70.
7. Kandzari DE, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. The Lancet 2018;391:2346-55.
8. Kandzari DE, Bhatt DL, Brar S, et al. Predictors of blood pressure response in the SYMPLICITY HTN-3 trial. Eur Heart J 2015;36:219-27.
9. Petrov I, Tasheva I, Garvanski I, Stankov Z, Simova I. Comparison of standard renal denervation procedure versus novel distal and branch vessel procedure with brachial arterial access. Cardiovasc Revasc Med 2019;20:38-42.
10. Pekarskiy SE, Baev AE, Mordovin VF, et al. Denervation of the distal renal arterial branches vs. conventional main renal artery treatment: a randomized controlled trial for treatment of resistant hypertension. J Hypertens 2017;35:369-75.
11. Fengler K, Ewen S, Hollriegel R, et al. Blood Pressure Response to Main Renal Artery and Combined Main Renal Artery Plus Branch Renal Denervation in Patients With Resistant Hypertension. J Am Heart Assoc 2017;6.
12. Bohm M. MG, Schmieder R., Schlaich M., Mahfoud F. Safety and efficacy measurements in the global SYMPLICITY registry. EuroIntervention 2017 (Euro17A-OP0338 (Abstract)).
13. Mahfoud F, Tunev S, Ewen S, et al. Impact of Lesion Placement on Efficacy and Safety of Catheter-Based Radiofrequency Renal Denervation. J Am Coll Cardiol 2015;66:1766-75.
14. Kiuchi MG, Schlaich MP, Chen S, et al. Relevance of Targeting the Distal Renal Artery and Branches with Radiofrequency Renal Denervation Approaches-A Secondary Analysis from a Hypertensive CKD Patient Cohort. J Clin Med 2019;8.
15. Azizi M, Sapoval M, Gosse P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. The Lancet 2015;385:1957-65.
16. Doltra A, Hartmann A, Stawowy P, et al. Effects of Renal Denervation on Renal Artery Function in Humans: Preliminary Study. PLoS One 2016;11:e0150662.
17. Id D, Bertog SC, Ziegler AK, et al. Predictors of blood pressure response: Obesity is associated with a less pronounced treatment response after renal denervation. Catheter Cardiovasc Interv 2016;87:E30-8.
18. Volz S, Spaak J, Elf J, et al. Renal sympathetic denervation in Sweden: a report from the Swedish registry for renal denervation. J Hypertens 2018;36:151-8.
19. Zweiker D, Lambert T, Steinwender C, et al. Effects of Renal Denervation Documented in the Austrian National Multicentre Renal Denervation Registry. PLoS One 2016;11:e0161250.
20. Fengler K, Rommel KP, Blazek S, et al. A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension (RADIOSOUND-HTN). Circulation 2019;139:590-600.

21. Schlaich MP, Sobotka PA, Krum H, Whitbourn R, Walton A, Esler MD. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. Hypertension 2009;54:1195-1201.
22. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med. 1984;311:819-823.
23. Brunner-La Rocca HP, Esler MD, Jennings GL, Kaye DM. Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure. Eur Heart J. 2001;22:1136-1143.
24. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in C-HeFT II. the V-HeFT VA Cooperative Studies Group. Circulation. 1993;87:VI40-48.
25. Kaye DM, Lefkovits J, Jennings GL, Bergin P, Broughton A, Esler MD. Adverse consequences of high sympathetic nervous activity in the failing human heart. J Am Coll Cardiol. 1995;26:1257-1263.
26. Petersson M, Friberg P, Eisenhofer G, Lambert G, Rundqvist B. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. Eur Heart J. 2005;26:906-913.
27. Brandt MC, Mahfoud F, Reda S, Schirmer SH, Erdmann E, Böhm M, Hoppe UC. Renal Sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. Journal of the American College of Cardiology. 2012;59:901-909.
28. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation. 2011;58:559-565.
29. Witkowski A, Pejbisz A, Florczak E, Kadziela J, Sliwinski P, Bielen P, Michalowska I, Kabat M, Warchol E, Januszewicz M, Narkiewicz K, Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. Hypertension. 2011;58:559-565.

16. Appendices

16.1. Contact Information

16.1.1. Coordinating Investigators

The following investigators will serve as Coordinating Investigators on the study:

Prof. Dr. David Lee
Stanford University Medical Center
300 Pasteur Drive
Stanford, California 94305
US

Prof. Dr. Andrew Sharp
Department of Cardiology
University Hospital of Wales
Heath Park Way
Cardiff, Wales
CF14 4CX
UK

16.1.2. Other contacts

A list with addresses of third parties, including the identification of the head of any core laboratory and the scope and duties to be entrusted is provided below. The sponsor will maintain a current list and it will be provided separately if updates from the below table are made.

Table 10: Other Contacts

Service Provider	Contact Information	Services	Scope and Duties Entrusted
Medtronic, Inc. (global sponsor)	3576 Unocal Place Santa Rosa, CA 95403 USA	Monitoring	Medtronic is responsible for the source data verification and compliance with the study CIP and applicable regulations (Monitoring); review and cleaning of the data (Data Management) and statistical programming and data analysis.
		Data management	
		Statistical programming and data analysis	

Service Provider	Contact Information	Services	Scope and Duties Entrusted
Beth Israel Deaconess Medical Center, Inc.	375 Longwood Avenue 3rd Floor Boston, MA 02215 USA Duane Pinto, MD	Angiographic core laboratory	The angiographic core laboratory is responsible for review and analysis of angiographic renal imaging to assess renal artery stenosis.
Cardiovascular Research Foundation (CRF)	1700 Broadway Floor 9 New York, NY 10019USA	Clinical events committee (CEC)	The CEC is an independent group whose primary responsibilities are to adjudicate any events that are part of study safety endpoints. The CEC will be composed of physicians who have experience in clinical studies in hypertension and/or cardiovascular indications.
		Data safety monitoring board (DSMB)	The DSMB is an independent group whose primary responsibility is to monitor the health, safety, and welfare of subjects. The DSMB will be composed of physicians who have experience in clinical studies in hypertension and/or cardiovascular indications and one biostatistician with experience in analysis of clinical trials.
Klinische Toxikologie Universitätsklinikum des Saarlandes	Klinische Toxikologie Universitätsklinikum des Saarlandes, Geb. 46 D-66421 Homburg (Saar) Germany Prof. Dr. Markus R. Meyer	Drug testing core laboratory	Drug testing core laboratory is responsible for processing and analyzing plasma and urine test samples to confirm the absence or presence of anti-hypertensive medications.
Medidata Solutions, Inc. (formerly known as Intelemage)	700 W. Pete Rose Way Suite 436 Cincinnati, OH 45203 USA	Media (i.e., imaging and file) upload	Provide platform to allow for the submission and management of files and study data/imaging studies.

Service Provider	Contact Information	Services	Scope and Duties Entrusted
Morristown Medical Center	Cardiovascular Core Lab Morristown Medical Center 100 Madison Avenue Morristown, NJ 07960 Linda D. Gillam, MD, MPH, FACC, FAHA, FESC, FASE	MRA/CTA core laboratory	The MRA/CTA core laboratory is responsible for review and analysis of the MRA/CTA renal imaging to assess renal artery stenosis.
VasCore – The Vascular Ultrasound Core Laboratory	The Vascular Ultrasound Core Laboratory 1 Bowdoin Square Tenth Floor Boston, MA 02114 USA Michael R. Jaff, D.O., RPVI	Renal artery duplex ultrasound (DUS) core laboratory	The DUS core laboratory is responsible for review and analysis of DUS renal imaging to assess renal artery stenosis.

16.1.3. List of participating investigational sitesand investigators

A list of investigational sites, IRBs and investigators will be provided under a separate cover.

16.2. Case Report Forms

A copy of the CRFs will be provided under a separate cover.

16.3. Sample Investigator Agreement

A sample investigator agreement will be provided under a separate cover.

16.4. Event Definitions

All-cause mortality: Death irrespective of cause.

Cardiovascular death: Any death due to immediate cardiac or vascular cause (e.g., sudden cardiac death, AMI, stroke, heart failure, fatal arrhythmia, or any procedure-related death).

Hospitalization for hypertensive crisis: Severely elevated blood pressure (BP), usually higher than 180/110 mm Hg, together with progressive or impending target organ damage, requiring in-patient

hospitalization and typically admission to the intensive care unit (ICU) (e.g., with parenteral [IV] antihypertensive medications), not related to confirmed nonadherence with medication or the protocol.

Non-cardiovascular death: Any death not covered by the above definition for cardiovascular death, including death due to infection, sepsis, pulmonary causes, accident, suicide, or trauma.

End-stage renal disease (ESRD): Two or more eGFR measurements <15 mL/min/m2 at least 21 days apart and requiring dialysis for one or more of the following:

- Volume management refractory to diuretics
- Hyperkalemia unmanageable by diet and diuretics
- Acidosis bicarbonate <18 unmanageable with HCO3 supplements
- Symptoms of uremia, nausea, vomiting

Major adverse events (MAE), defined as a composite of the following events:

- All-cause mortality
- ESRD
- Significant embolic event resulting in end-organ damage (e.g., kidney/bowel infarct, lower extremity ulceration or gangrene, or doubling of serum creatinine documented by at least two measurements at least 21 days apart)
- Renal artery perforation requiring reintervention
- Renal artery dissection requiring intervention
- Vascular complications
- Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications
- New renal artery stenosis > 70%, confirmed by angiography by the angiographic core lab

Major bleeding according to TIMI definition: Intracranial hemorrhage; ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within seven days of the procedure)

Myocardial infarction (MI): MI is defined as the concurrent documentation of two of the three elements listed below in the appropriate clinical circumstance:

1. Chest pain or ischemic equivalent
2. New pathologic q waves in at least 2 contiguous ECG leads
3. Cardiac biomarker elevation by any of the definitions below:

Appropriate cardiac enzyme data (respecting top-down hierarchy):

a) CK greater than or equal to 2* URL confirmed by:

- CKMB > l*URL *or*
- in the absence of CKMB: Troponin > l*URL *or*

b) in the absence of CK:

- CKMB > 3*URL
- In the absence of CK and CKMB: Troponin > 3*URL
- In the absence of CK, CKMB and Troponin, clinical decision based upon clinical scenario

New renal artery stenosis: Greater than 70% renal artery stenosis confirmed by analysis of angiography by the core lab. If core lab analyses are unavailable, site reported analysis may be used. The date of the event will be the date of confirmatory angiography.

Renal artery dissection: Creation of a false lumen between the layers of the artery requiring intervention.

Renal artery perforation: Puncture creating a hole in the vessel wall requiring intervention.

Renal artery reintervention: Interventional procedure performed on the renal artery following completion of the renal denervation procedure and removal of the guide catheter.

Significant embolic event: Sudden obstruction of a blood vessel by debris (i.e., blood clot, plaques, fat, bacterial mass, cancer cells, or air bubbles) resulting in end-organ damage. Examples include:

- Kidney/bowel Infarct: necrosis (cell death) of an area of tissue in all or part of the organ due to cessation of the blood supply due to stenosis or occlusion
- Lower extremity ulceration: a non-healing lesion on a body surface (i.e., skin, mucous membrane)
- Gangrene: necrosis of tissue usually resulting from deficient or absent blood supply
- Doubling of serum creatinine confirmed by at least two measurements over 21 days apart
- DOES NOT INCLUDE MI OR STROKE WHICH ARE ADJUDICATED SEPARATELY

Stroke: Sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria, or other focal neurological deficits due to vascular defects in the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persists more than 24 hours.

Vascular Complications: Complications that require surgical repair, interventional procedure (not including manual compression), thrombin injection, or blood transfusion (requiring more than 2 units of packed red blood cells within any 24-hour period during the first 7 days post-procedure); possible vascular complications are as follows:

- Clinically significant groin hematoma: swelling due to the accumulation of blood around an organ, tissue or space caused by the leakage of blood from a vessel
- Arteriovenous fistula: formation of an abnormal connection between an artery and a vein
- Pseudoaneurysm: a hematoma that forms as the result of a leaking hole in an artery. Note that the hematoma forms outside the arterial wall, so it is contained by the surrounding tissues. Also, it must continue to communicate with the artery to be considered a pseudoaneurysm
- Excessive Bleeding: requires >2 units of packed red blood cells (PCRB) within any 24-hour period during the first 7 days post-randomization and documented bleeding

16.5. Blood Pressure Measurement Procedures

16.5.1. Office Blood Pressure

All office blood pressure (OBP) measurements must be taken with the automatic blood pressure monitor as specified by the sponsor.

- At Screening Visit 1 (SV1), the appropriate arm for study measures must be selected as specified in **section A** below and used for all subsequent follow-up visits.
- All study visits should begin before 10:30 am, with the following exceptions:
  - SV1, if the subject is consented at SV1
  - Unscheduled follow-up visits
  - medication reintroduction visits
  - the discharge visit.

Subjects should not take antihypertensive medication the morning of the visit, but rather bring their medications to the visit. Pill taking should be observed after the OBP measurement (if applicable), or in the case of in-home, virtual or telephone visits, the subject should delay taking antihypertensive medication until the blood pressure measurement is completed.

A. <u>ARM SELECTION AT SCREENING VISIT 1 (SV1) ONLY</u>

1) If the subject is taking antihypertensive medications, the visit should begin before 10:30 am. If the subject normally takes their anti-hypertensive medication(s) in the afternoon, the visit may occur in the afternoon.
2) With the subject prepped per "Preparation" **section B** below, measure BP in each arm. Ensure each measurement is recorded and identify on which arm the BP was measured.
3) Use the arm with the higher systolic BP for screening measurements and all subsequent study-required measurements
   a. If there is a reason to use a particular arm, document the reason, and use that arm for all measurements.

B. <u>PREPARATION AT ALL VISITS</u>

1) Ensure the BP monitor and all necessary equipment are functioning correctly (per sponsor instructions).
2) Confirm the subject did not drink coffee or alcohol, smoke, or exercise, within 30 minutes prior to taking BP measurements.
3) Request that the subject use the bathroom prior to taking BP measurements (a full bladder can affect the reading).

4) The subject should be seated comfortably with the back supported, the upper arm bared with no clothing between the arm and BP cuff. The legs should **not** be crossed.

5) Ensure that the BP cuff is appropriately sized (see **Table 11** below) and that the upper arm is supported at the level of the heart (e.g., resting on a table at the level of the subject's heart). The same cuff size should be used as selected at SV1 for the remainder of the study.

Table 11: BP Cuff Size Chart

Cuff Size*	Fits Arm Circumference of (inches)	Fits Arm Circumference of (centimeters)
Small	7 – 9	17 – 22
Medium-Large	9 - 17	22 - 42

*If a subject is on the border of two cuff sizes, opt for the larger of the two sizes
**Subjects requiring greater than a large cuff size at time of screening must be excluded from the study (screen failure).

6) Perform a "test" BP measurement. Ensure test measurement is recorded.

7) Have the subject sit comfortably and quietly for at least five minutes, but no more than 10 minutes, with back supported and feet flat on the ground (i.e., not on an exam table, legs not crossed) prior to proceeding with the actual BP measurement.

C. METHOD FOR TAKING BP AT ALL VISITS

1) General Instructions

   a. With subject prepared per **section B** above and using arm selected at SV1, take at least three (3) seated BP measurements in order to obtain the BP average.

   b. Wait at least one (1) minute between each BP measurement. **Ensure that the same time clock is used for tracking the time intervals to avoid deviations due to insufficient wait time between measurements.**

   c. Document and label after each measurement.

2) **Three (3) consecutive, consistent seated** blood pressure measurements must be used to obtain the blood pressure average.

   a. If the lowest and highest systolic BP (SBP) values of the first three consecutive BP measurements are >15 mmHg apart, take one additional reading and average the last three consecutive measurements (measurements 2-4).

b. If the measurements are still >15 mmHg apart, take one additional reading and average the last three consecutive measurements (measurements 3-5).

c. If the measurements are still >15 mmHg apart, take one final measurement and average the last three consecutive measurements (measurements 4-6).

3) **At screening visits:** If the lowest and highest SBP values for the readings are >20 mmHg apart after six measurements, the subject must be excluded from the study (screen failure).

4) **At all subsequent follow-up visits:** If the lowest and highest SBP values for the readings are >20 mmHg apart after six measurements, take the average of the last three measurements (measurements 4 – 6) and record the value on the CRF.

5) Record the **last** three consecutive, consistent readings on the CRF (do not pick the 'best' three).

16.5.2. Orthostatic Hypotension Evaluation (SV2 ONLY)

In addition to the seated OBP recordings above, measure supine and standing BP at **SV2 only**.

1) Have the subject lie supine for at least five minutes prior to taking the supine BP measurement.

2) Measure BP within 1-3 minutes upon standing for the standing measurement. Standing must follow the supine to measure orthostatic effect.

3) Evaluate for any symptoms (e.g., dizziness) that may occur within three minutes after standing.

16.5.3. Ambulatory Blood Pressure Monitoring

1) All 24-hour ABPM measurements must be taken with the 24-hour ABPM device provided by the sponsor to ensure consistency.

2) Cuff size identified at SV1 should be used for the duration of the study.

3) If the subject is on antihypertensive medications, the visit should begin before 10:30am. If the subject normally takes antihypertensive medication in the afternoon, the subject visit may occur in the afternoon.

4) Study personnel should observe the subject swallowing the antihypertensive medication(s), if applicable (or verbally confirmed in the case of a phone or virtual visit).

5) Once medication consumption is completed and documented, the ABPM device should be applied to the subject and the recording started before the subject leaves the office (or completes the call in the case of a phone or virtual visit).

6) Place cuff on the subject's non-dominant arm.

7) Instruct the subject in proper cuff positioning in case they must remove it but stress the importance of leaving the BP cuff on.

    a. The ABPM has pre-set parameters and should not be adjusted. These parameters are set to record BP every 30 minutes.

8) Instruct the subject:

    a. To engage in their usual level of physical activity, but to avoid strenuous exercise during the monitoring period,

    b. To hold the arm still by the side while the device is taking a reading

9) Upon the return of the ABPM machine:

    a. Submit the 24-hour ABPM data to Medtronic

    b. A 24-hour ABPM will be considered adequate if the number of successful daytime readings captured is ≥21 and the number of successful nighttime readings captured is ≥12.

    c. At SV2, a single repeat ABPM will be allowed in case of the following:

        - The 24-hr systolic ABPM measured is between 135 - <140 mmHg or 170-175 mmHg
        - A valid number of readings is not obtained
        - There is a technical issue with the BP monitor or failure to follow the ABPM instructions

    d. In all other instances at SV2, the ABPM will not be allowed to be repeated and the subject will be considered a screen failure.

    e. For all other time points with ABPM, make all efforts to obtain repeat ABPM from subject until the minimum number of readings is obtained.

17. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Marianne Wanten, Sr. Clinical Research Manager
2.0	• Implemented 6 months follow-up renal imaging • Added bicarbonate to Chem-7 panel • Added 2 week in-person follow-up visit • Added 6 and 10 week phone follow up	Marianne Wanten, Sr. Clinical Research Manager
3.0	• Added alternate follow-up methods to allow more flexibility during extenuating circumstances, such as a global pandemic in section 9.1.6 • Implemented ISO14155 updates • Added safety event definitions in section 16.4 • Added Statement that study will be registered on CT.gov in section 7.1 • Added Clarification regarding renal imaging not obtained at 6 month follow-up visit in section 9.1.6 • Clarification added for taking anti-hypertensive medication in cases of in-home, virtual or telephone visit in section 16.5 • Clarification to verbally confirm subject's medication use in cases of telephone visits in section 16.5	Marianne Wanten, Sr. Clinical Research Manager
4.0	• Remove sentence in section 9.1.6. "These alternative methods have no potential impact on patient safety, do not affect data integrity and do not introduce study bias Add changes."	Yuliya Korytchenko, Clinical Research Specialist
5.0	Update to CIP v5, to align with the ISO14155 2020 guidelines, EU MDR requirements and to incorporate CIP clarification letter updates. These changes have no potential impact on performance, effectiveness, safety or other study endpoints nor any affect to study documents. **For clarification purposes:** • Update Glossary, remove unused terms, add missing terms • Add EUDAMED number to Synopsis per ISO requirements • Update 'Lead Principal Investigator' to 'Coordinating Investigator' throughout for consistency • Clarified Role of the Sponsor • Reformat of Tables 1, 2, 3, 4 for clarity • Update study duration, number of sites, enrollment timelines	Marina Ostanniy, Pr Clinical Research Specialist

Version	Summary of Changes	Author(s)/Title
	• Update AE and DD reporting requirements • Remove MDD 93/42/ECC • Clarify follow-up visit requirements (9.1.6) • Add definitions for malfunction, product complaint, • Add AE classification responsibilities • Add product complaint reporting requirements • Update AE reporting requirements per EU MDR requirements • Update reference to EC/IRB for consistency throughout • Update co-investigator to sub-investigator • Update event definitions to match CEC Charter • Update Section 16.5 Blood Pressure Measurement Procedures for clarity • Added CIP template vC requirements • **Administrative updates:** • Update formatting throughout for consistency and clarity; update word 'patient' to 'subject throughout; • Correct grammar and punctuation throughout • Update formatting of Tables 1, 2, 3, 4 for clarity • Format sub-headings for consistency throughout • Remove generic phone number, updated contact for study information • Add Table of Tables and Table of Figures • Updates per MDT style guide throughout	