SPYRAL PIVOTAL – SPYRAL HTN-OFF MED

Clinical Investigation Plan

Version 12.0

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Change History record

Version History		
Version	**Summary of Changes**	**Author**
1.0	*Initial*	Vanessa DeBruin
2.0	*Changes include the list below:* *1. Updated Time Course* *2. Addition of the Medtronic SEEQ™ Mobile Cardiac Telemetry (MCT) System* *3. Revisions of exclusion criteria* *4. Updated/clarified safety and efficacy endpoints* *5. Added baseline duplex ultrasound if obtained per standard of care* *6. Updated anti-platelet/anti-coagulation language* *7. Added Drug testing for Hypertensive Crises* *8. Added/revised adverse event reporting language in Japan and Australia* *9. Added contact information for the services providers* *10. Updated Blood Pressure Measurement Procedures* *11. Added list of Appendices* *12. Minor formatting, typo, and clarifying language changes throughout protocol*	Vanessa DeBruin
3.0	*Changes include the list below:* *1. Updated approval signatories* *2. Updated Time Course* *3. Updated total number of subjects to be screened from 400 to 700* *4. Revisions of inclusion and exclusion criteria* *5. Clarified study ISO14155:2011 compliant except for AEs not reported for Control subjects after 12 months post-randomization* *6. Updated Section E.6 Study device/product traceability* *7. Updated Section F Study Methods* *8. Revised Figure 8 for consistency with protocol changes* *9. Added CT/MRA Service Provider on Section L.1.1* *10. Updated Section L.7 Blood Pressure Measurement Procedures* *11. Minor formatting, typo, and clarifying language changes throughout protocol*	Vanessa DeBruin
4.0	*1. Updated approval signatories* *2. Updated Time Course*	Vanessa DeBruin

	3. Updated total number of subjects to be screened from 700 to approximately 750 to align with increase in number of subjects randomized *4. Updated total number of subjects to be randomized to state up to 170* *5. Added 'drug naïve subjects' only when referring to the diastolic blood pressure reason for screen failure at the 2 week screening visit for Figure 8.* *6. Removed "non-fasting" when referring to blood draws* *7. Clarified when crossover will be determined* *8. Added "Updated address for Cardiovascular Research Foundation* *9. Removed statement that a 6 French sheath should be used for renal angiogram*	
4.1	*1. Corrected pagination errors caused by conversion from word to Portable Document Format*	Vanessa DeBruin
5.0	*1. Updated approval signatories* *2. Updated number of participating centers to "up to 50".*	Vanessa DeBruin
6.0	*Changes include the list below:* *1. Updated Approval Signatories* *2. Updated Regional Sponsors* *3. Updated Time Course* *4. Added Canada, Including Regulations And Adverse Event Reporting Language* *5. Updated Total Number Of Subjects To Be Screened From 750 To 1800* *6. Updated Total Number Of Subjects To Be Randomized To Approximately 433* *7. Revisions Of Inclusion And Exclusion Criteria* *8. Updated/Clarified Safety And Efficacy Endpoints* *9. Removal Of The Medtronic SEEQ™ Mobile Cardiac Telemetry (MCT) System* *10. Addition Of 24 Month Renal Duplex Ultrasound (DUS)* *11. Updated Training Requirements* *12. Updated Procedure Section* *13. Addition Of SF36 Survey (Quality Of Life)* *14. Updated Visit Windows* *15. Updated Sample Size* *16. Addition Of Lipid Panel (Total, High-Density Lipoprotein Cholesterol, Low-Density Lipoprotein Cholesterol, Total Cholesterol),Uric Acid And High-Sensitivity CRP (Hs-CRP) Laboratory Tests* *17. Updated Clinical Experience Section* *18. Updated Supply Of Investigational Devices/Products Section* *19. Revision Of The Follow-Up Schedule* *20. Updated Data Analysis And Reporting* *21. Medication Titration Section Replaced With Medication Re-Introduction For Subjects With 3M Office Systolic Blood Pressure (SBP)≥ 140 mmhg Section* *22. Clarified Crossover Process*	Marina Ostanniy

	23. Updated Unavoidable Adverse Events Table *24. Updated Adverse Event Reporting Requirements Table* *25. Added 24 Month Duplex Ultrasound Requirement* *26. Revision of the QOL surveys administration schedule* *27. Updated Blood Pressure Measurement Procedures* *28. Revised Figures And Tables Throughout Protocol For Consistency With Protocol Changes* *29. Updated List Of Providers (Section L.1.1)* *30. Minor Formatting, Typo, And Clarifying Language Changes Throughout Protocol*	
7.0	*Changes include the list below:* *1. Replacement of 24 Month Renal Duplex Ultrasound (DUS) with 12 Month Renal Imaging and Updated Number of 12 M Images From 50 to "a minimum of 100 and up to 433" Throughout Protocol.* *2. Added "≥40% Decline In eGFR" as a Secondary Safety Endpoint* *3. Added Renal Artery Stenosis Evaluation at 12 Months to Data Analysis And Reporting* *4. Updated References* *5. Minor Formatting, Typo, And Clarifying Language Changes Throughout Protocol* *6. Updated Figure 10 with visit requirements.*	Marina Ostanniy
8.0	*1. Clarify that subjects who have already completed their 12 month follow-up at time of protocol approval will be required to undergo renal imaging at their next scheduled follow-up unless they have a renal angiogram due to crossover.* *2. Added clarification on medication re-introduction visits between 3 and 6 months follow-up.* *3. Minor Formatting, Typo, And Clarifying Language Changes Throughout Protocol* *4. Updated Figure 10 with visit requirements* *5. Added clarification to Crossover process* *6. Updated Study Name*	Vanessa DeBruin
9.0	*1. Update to clarify that SV1 can occur after 10:30am, if Informed Consent Form is signed at SV1.* *2. Update to clarify medications use prior to consent at SV1* *3. Update F.10 Crossover Procedures to align with Table 2* *a. EQ-5D and SF-36: not needed at Crossover Baseline.* *b. Drug testing and witness pill taking requeded at Baseline* *4. Update F.7 Follow-Up Procedures and F.10 Crossover Procedures to clarify that when the ABPM is repeated, office blood pressure and drug testing must be repeated on day the ABPM is applied before each repeated ABPM* *5. Update to clarify that High-sensitivity CRP is not required to be measured for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed* *6. Exclusion criteria #1: added that patients who received catheter or surgical treatment for Atrial Fibrillation and are in sinus rhythm are not excluded.*	Marina Ostanniy

	7. *Exclusion criteria #14: update to state 'Individual who requires more than occasional use (e.g. PRN) of narcotic drugs over the month prior to Screening Visit 1.'* 8. *Exclusion Criteria #17: indicate that subjects need to be off NSAIDS for 1 month prior to SV2, not enrollment.* 9. *Updated statistics section, including sample size section and interim analyses to reflect change* 10. *Updates to reflect OBP device without printer* 11. *Updated reasons when ABPM can be repeated to include if ABPM guidelines were not followed.* 12. *Clarification added around cuff size for OBP and ABPM* 13. Updated with most recent clinical data 14. *Added/revised adverse event reporting language in Australia* 15. *Minor formatting, typo and clarifying language changes throughout the protocol*	
10.0	*1. Updated Section E7 to include alternate Follow-up methods to allow more flexibility during extenuating circumstances, such as a global pandemic.* *2. 12-month imaging requirements clarified for UK and German subjects.3. Incorporated latest version of ISO14155 updates* *3. Formatting and administrative updates*	Pamela McKenna
11.0	*1. Administrative update to remove the following sentence from the section E.7 'Follow-up Procedures'. 'These alternative methods have no potential impact on patient safety, do not affect data integrity and do not introduce study bias.' This sentence was added in version 10.0 of the CIP which was not implemented prior to version 11.0.*	Pamela McKenna
12.0	*1. Administrative update to align heading lettering with prior CIP versions.*	Pamela McKenna

TABLE OF CONTENTS

A SYNOPSIS

Title

Global Clinical Study of Renal Denervation with the Symplicity Spyral™[i] multi-electrode renal denervation system in Patients with Uncontrolled Hypertension in the Absence of Antihypertensive Medications.

Purpose

The purpose of this study is to test the hypothesis that renal denervation decreases blood pressure and is safe when studied in the absence of antihypertensive medications.

Design

Multi-center, international, prospective, single blinded, 1:1 randomized, interventional, sham-controlled study.

Medical device/product

The Symplicity Spyral™ multi-electrode renal denervation catheter (Symplicity Spyral™ catheter) and the Symplicity G3™ renal denervation RF generator (Symplicity G3™ generator) will be used in this clinical study. These components of the Symplicity™ renal denervation system are investigational in the United States, Canada and Japan (referred to as MDT-2115). Both the Symplicity Spyral™ catheter and Symplicity G3™ generator are commercially available in Australia and countries where CE-mark applies. Additional geographies may be added to the clinical study and the approval status will be documented under a separate cover.

Objective

The objective of this study is to test the hypothesis that renal denervation is safe and reduces systolic blood pressure (SBP) in patients with uncontrolled hypertension compared to a sham-controlled population, in the absence of antihypertensive medications. In this study, “uncontrolled hypertension” is defined as an office systolic blood pressure (SBP) ≥ 150 mmHg and <180 mmHg, an office Diastolic Blood Pressure (DBP) ≥90 mmHg and a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) average SBP ≥140 mmHg to <170 mmHg, all of which are measured at Screening Visit 2 (per Appendix L7). Data obtained without the confounding presence of antihypertensive medications will be used to confirm the effect of renal denervation on elevated blood pressure. The data collected in this study will be used to support regulatory submissions around the world to obtain market approval for the Symplicity Spyral™ multi-electrode renal denervation catheter (Symplicity Spyral™ catheter) and the Symplicity G3™ renal denervation RF generator, from regulatory entities, including, but not limited to: the Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, and the U.S. Food and Drug Administration (FDA).

[i] Trademarks may be registered and are the property of their respective owners.

Primary Endpoints

There are two primary endpoints in this study (one safety and one efficacy). The study will be considered successful if both the primary safety and efficacy endpoint hypotheses are met.

Powered Primary Safety Endpoint

- Incidence of Major Adverse Events (MAE), defined as a composite of the following events, through one-month post-randomization (6 months for new renal artery stenosis)
  - 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 laboratory

Powered Primary Efficacy Endpoint

- Baseline adjusted change (using Analysis of Covariance) in systolic blood pressure (SBP) from baseline (Screening Visit 2) to 3 months post-procedure as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM).

Secondary Endpoints

Powered Secondary Efficacy Endpoint

- Baseline adjusted change (using Analysis of Covariance) in office systolic blood pressure from baseline (Screening Visit 2) to 3 months post-procedure.

Secondary Safety Endpoints

- Acute/Procedural Safety Secondary Endpoints – Compared Between Groups at 1 Month Post-Procedure:
  - Significant embolic event resulting in end-organ damage
  - Renal artery perforation requiring intervention
  - Renal artery dissection requiring intervention
  - Vascular complications
  - End-Stage Renal Disease
  - ≥40% decline in eGFR
  - New Myocardial Infarction

  - New Stroke
  - Renal artery re-intervention
  - Major bleeding according to TIMI definition (i.e. intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)
  - Increase in serum creatinine > 50% from Screening Visit 2
  - New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core laboratory
  - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol

- Chronic Safety Secondary Endpoints – Compared Between Groups at 3, 6, 12, 24, and 36 Months Post- Randomization:
  - All-cause mortality
  - End-Stage Renal Disease
  - ≥40% decline in eGFR
  - New Myocardial Infarction
  - New Stroke
  - Renal artery re-intervention
  - Major bleeding according to TIMI definition (i.e. intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)
  - Increase in serum creatinine > 50% from Screening Visit 2
  - New Renal artery stenosis >70%, confirmed by angiography and as determined by the angiographic core laboratory
  - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol
- Secondary Efficacy Endpoints – Compared Between Groups
  - Change in systolic blood pressure (SBP) from baseline (Screening Visit 2) as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM) at 3, 6, 12, 24 and 36 months post-procedure.
  - Change in office systolic blood pressure from baseline (Screening Visit 2) at 1, 3, 6, 12, 24 and 36 months post-procedure.
  - Incidence of achieving target office systolic blood pressure (SBP <140 mmHg) at 1, 3, 6, 12, 24 and 36 months post-procedure.
  - Change in office diastolic blood pressure from baseline (Screening Visit 2) at 1, 3, 6, 12, 24 and 36 months post-procedure.
  - Change in diastolic blood pressure from baseline (Screening Visit 2) as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM) at 3, 6, 12, 24 and 36 months post-procedure.

- Summary of Quality of Life (QOL) Measures (EQ5D and SF36)

Additional analyses

The following additional analyses will be conducted:

- Antihypertensive medication usage throughout the study, including escape subjects prior to 3-months and subjects reintroduced to medications after 3 months

- Additional procedural characteristics e.g. treatment duration, frequency of distal renal artery treatment, ablations per vessel, location of ablations, number of ablations per patient and other characteristics will be analyzed to assess their impact on blood pressure.

Subject population

Patients with uncontrolled hypertension will be enrolled in accordance with the Inclusion and Exclusion criteria specified in the protocol. Approximately 1800 subjects will be screened in order to randomize a total of approximately 433 subjects; this includes up to 80 subjects used as an informative prior (see Section C.6). The study will be conducted at up to 50 study centers in the United States, Japan, Australia, Canada and countries where CE mark applies. Additional geographies may be added to the clinical study at a later date and the approval status will be documented under a separate cover. Enrollment is expected to take approximately 33 months. Subjects may participate in the study from the time of signing consent until completion of three years of follow-up after procedure as described in Table 1 through Table 3. Control (sham) subjects may be offered renal denervation therapy (crossover) after their-6 month follow-up visit and will be followed-up for two years, according to Table 2.

Screening Criteria

Eligible patients will be screened for participation into the study if they are aged between 20-80 years, have a diagnosis of hypertension, and whom, in the judgment of the investigator, will have a blood pressure within the range required for randomization (ABPM SBP ≥140 mmHg and <170 mmHg, office SBP ≥ 150 mmHg and <180 mmHg and office DBP ≥90 mmHg measured according to guidelines in Appendix L.7) in the absence of antihypertensive medications or following antihypertensive medication withdrawal.

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 DBP ≥90 mmHg measured at Screening Visit 2, according to the guidelines in Appendix L.7.

3. Individual has a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) average SBP ≥140 mmHg and <170 mmHg measured at Screening Visit 2 according to guidelines in Appendix L.7: ABPM is considered valid if the number of successful daytime readings captured is ≥ 21 and the number of successful nighttime readings captured is ≥ 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 three-month post-procedure visit.

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 renal artery anatomy that is ineligible for treatment including:
    a. Main renal artery for each kidney less than 3mm or greater than 8mm
    b. Lacks a main renal arterial vessel (greater than 3mm and less than 8mm in diameter) for each kidney that does not allow 4 simultaneous quadrantic (4SQ) radio frequency ablations in the main renal artery or equivalent (defined as 4SQ ablations in all branch vessels greater than 3mm and less than 8mm)
4. Presence of FMD (defined as visible beading of the artery on angiography).
5. Has >50% stenosis in any treatable vessel.
6. Has a renal artery stent placed <3 months prior to the denervation procedure.
7. Presence of an aneurysm defined as any localized increase in the diameter of the vessel.
8. Treatment area within 5mm of a segment in the renal artery which contains any of the following:
    a. Atheroma,
    b. Calcification, or
    c. Renal artery stent
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 patient is black) x 0.742 (if female)). (Note: an eGFR calculation specific to Japanese patients will be used for subjects enrolled in Japan).
10. Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%.
11. Individual is taking SGLT2 inhibitors or GLP-1 agonists that have been prescribed < 90 days prior to Screening Visit 1 or who does not plan to remain 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 of ≥20 mmHg or DBP of ≥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 who requires more than occasional use (e.g. PRN) of narcotic drugs over the month prior to Screening Visit 1.

15. Individual has documented primary pulmonary hypertension.

16. Individual has an 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 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 upper 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.

Treatment

Following Screening Visit 1 (SV1), eligible subjects will undergo a minimum of three and a maximum of four weeks of an antihypertensive medication (anti-HTN meds) washout period. If at any time the average of 3 seated office Blood Pressure (OBP) readings results in a SBP ≥180 mmHg, the subject will be considered a screen failure and will be exited from the study, and anti-HTN meds will be restarted at the investigator's discretion.

Subjects who continue to meet eligibility criteria will return for Screening Visit 2 (SV2). Subjects who were not previously treated with anti-HTN meds and subjects who had discontinued anti-HTN meds for minimum of four weeks prior to SV1 (considered drug naïve) will also return for Screening Visit 2 within three to four weeks. Subjects who continue to meet eligibility criteria after completion of Screening Visit 2 and who have received randomization approval by the Sponsor will be randomized.

The renal denervation or control procedure will occur within a maximum of two weeks (14 calendar days) following completion of Screening Visit 2.

Following the renal denervation or control procedure, subjects will be followed at 2, 4, 6, 8, 10 weeks and 3M post-procedure.

At any time, if the subject's office SBP ≥180 mmHg as measured per protocol with a confirmatory BP measurement within 72 hours, the subject can be put back on an anti-HTN medication regimen per the investigator's discretion. If possible, but at the discretion of the investigator, the subject will be asked to wear the 24h ABPM and have blood drawn for a Chem 7 panel, and antihypertensive drug testing, and urine collected for antihypertensive drug testing, prior to being put back on medications. The subject will then be exited from the off-medication portion of the study and will be followed according to instructions listed in Table 3. At the three months (90 days) follow-up, after office and valid ambulatory blood pressure measurements are obtained, subjects will be reintroduced to standard medical therapy, if required, according to Section F.9.

All subjects will be followed annually through 36 months post procedure (Table 1), except Crossover subjects. Subjects and blinded study personnel will be unblinded to the randomization assignment at 6 months. Control (sham) subjects may be offered renal denervation therapy (crossover) after their 6-month follow-up visit, according to Section F.10. Crossover subjects will return for office visits at 1, 3, 6, 12 and 24 months post-renal denervation procedure (Table 2).

Interim Analyses

Interim analyses will take place after 210 and 240 subjects (excluding the first consecutively randomized 80 subjects in the SPYRAL HTN-OFF MED study) have 3-month efficacy endpoint data available. This will require randomizing approximately 247 and 282 subjects to account for attrition. A decision to stop or continue the study will be made after each interim analysis has been reviewed. If the study does not stop at an interim analysis, randomization will continue to the maximum study size of N=300 evaluable subjects (requiring approximately 353 randomized subjects to account for attrition).More details on the interim analyses can be found in the study Statistical Analysis Plan.

Time Course

Start of enrollment (consent): June 2015

Planned completion of randomization: November 2019

Planned study close-out: April 2023

Clinical Procedures

Table 1: Schedule of Testing for All Subjects *(See Table 2 for Crossover Subjects' Testing)*

3 Months (90 days): 76-104 days - 4 Months (120 days):113 -127 days - 6 Months (180 days): 166-194 days - 12 Months (360 days): 330-390 days - 24 Months (720 days): 690-750 days - 36 Months (1080 days): 1050-1110 days

Post-Procedure

(Wk= ± 3 days) (M=months ± 14 days for 3M and 6M visits; ±7 days for 4M visit; ± 30 days for 12M-36M visits)

Required Assessments	SV1	3 Wk Washout (minimum) with screening visit at Wk 2 (see next column)	2 Wk visit (Screening) ± 3 days	SV2 (within 3-4 wk of SV1)	Procedure	Prior to Discharge	2 Wk	4 Wk	6 Wk	8 Wk	10 Wk	3M	4M visit for BP≥140 mmHg at 3M (± 7 days)	6M	12M	24M	36M
Medical History	X																
Clinical assessment			X	X			X	X	X[3]	X	X[3]	X	X	X	X	X	X
Medications prescribed according to section F.9 if SBP ≥ 140 mmHg												X	X				
Witnessed pill intake (if subject is taking antihypertensive medications), Complete after OBP measurements.														X	X	X	X
Renal Denervation or Sham Procedure					X												

3 Months (90 days): 76-104 days - 4 Months (120 days):113 -127 days - 6 Months (180 days): 166-194 days - 12 Months (360 days): 330-390 days - 24 Months (720 days): 690-750 days - 36 Months (1080 days): 1050-1110 days

							Post-Procedure (Wk= ± 3 days) (M=months ± 14 days for 3M and 6M visits; ±7 days for 4M visit; ± 30 days for 12M-36M visits)									
Required Assessments	**SV1**	**3 Wk Washout (minimum) with screening visit at Wk 2 (see next column)**	**2 Wk visit (Screening) ± 3 days**	**SV2 (within 3-4 wk of SV1)**	**Procedure**	**Prior to Discharge**	**2 Wk**	**4 Wk**	**6 Wk**	**8 Wk**	**10 Wk**	**3M**	**4M visit for BP≥140 mmHg at 3M (± 7 days)**	**6M**	**12M**	**24M**	**36M**
Office Blood Pressure according to guidelines in Appendix L.7	X		X	X		X	X	X	X[3]	X	X[3]	X	X	X	X	X	X
24-Hour ABPM according to guidelines in Appendix L.7				X								X		X	X	X	X
Blood Tests (uric acid, lipid panel and high-sensitivity CRP (hs-CRP)[7]				X													
Blood Tests (Chem-7)[4]				X		X		X				X		X	X	X	X
Blood Tests (renin and aldosterone)				X								X					
Serum or Urine Pregnancy Test				X													
Drug testing				X								X	X	X	X	X	X

							Post-Procedure (Wk= ± 3 days) (M=months ± 14 days for 3M and 6M visits; ±7 days for 4M visit; ± 30 days for 12M-36M visits)									
3 Months (90 days): 76-104 days - 4 Months (120 days):113 -127 days - 6 Months (180 days): 166-194 days - 12 Months (360 days): 330-390 days - 24 Months (720 days): 690-750 days - 36 Months (1080 days): 1050-1110 days																
Required Assessments	**SV1**	**3 Wk Washout (minimum) with screening visit at Wk 2 (see next column)**	**2 Wk visit (Screening) ± 3 days**	**SV2 (within 3-4 wk of SV1)**	**Procedure**	**Prior to Discharge**	**2 Wk**	**4 Wk**	**6 Wk**	**8 Wk**	**10 Wk**	**3M**	**4M visit for BP≥140 mmHg at 3M (± 7 days)**	**6M**	**12M**	**24M**	**36M**
Renal Artery Imaging - Angiogram					X												
Renal Artery Imaging				X[5]										X[1]	X[6]	(X)[6]	(X)[6]
Blinding Assessment						X						X		X			
EQ-5D and SF-36				X								X		X	X	X	X
Mortality Assessment[2]							X	X		X		X		X	X	X	X
Medication Review, Event Review	All adverse events (AE) and medication review After 12 months, previously reported AEs will need to be reviewed and updated as needed.															Serious AE and all medication review	

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. The 6M DUS will not be required for subjects crossing over at 6M visit.

2 Conduct if follow-up missed.

3 If medically necessary, phone contact may be replaced with office visit. Office blood pressure (according to guidelines in Appendix L.7), only needs to be obtained if an office visit occurs.

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

5 Submit baseline duplex ultrasound, CT, or MRA if obtained per standard of care within one year from the date of Screening Visit 16 DUS/CTA/MRA required as first line imaging modality at 12M (and 24M and 36M as applicable). Repeat DUS, MRA, or CTA to be used if prior imaging modality is nondiagnostic. If repeat DUS/CTA/MRA is nondiagnostic or evidence of a clinically significant stenosis (>60-70%) is indicated, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month without renal imaging will be required to undergo renal imaging at their next scheduled follow-up unless they have a renal angiogram due to crossover. For participating sites in Germany and the UK, only DUS or renal MRA imaging at the 12-month follow-up visit (or 24 or 36M follow-up as applicable) will be performed. For these countries, if the initial DUS or initial renal MRA is non-

diagnostic, a repeat DUS or repeat renal MRA should be performed. If the initial imaging modality or subsequent repeat(s) are non-diagnostic, the investigator should choose the repeat imaging modality (DUS or MRA) that is expected to yield the required information for a diagnostic study.
7 High-sensitivity CRP is not required to be measured for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed.

Table 2: Schedule of Testing for Crossover Subjects

1 Month: 14 – 44 days 3 Months: 76-104 days - 6 Months: 166-194 days - 12 Months: 330-390 days - 24 Months: 690-750 days				**Post-Procedure** **(M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-24M visits)**				
Required Assessments	**Baseline**	**Renal Denervation**	**Prior to Discharge**	**1M**	**3M**	**6M**	**12M**	**24M**
Clinical assessment	X			X	X	X	X	X
Blood Tests (Chem-7)***	X		X	X	X	X	X	X
Blood Tests (uric acid, lipid panel and high-sensitivity CRP (hs-CRP))******		X (prior to procedure)*****						
Office Blood Pressure according to guidelines in Appendix L.7	X		X	X	X	X	X	X
Witnessed pill intake (if subject is taking antihypertensive medications), Complete after OBP measurements.	X				X	X	X	X
Serum or Urine Pregnancy Test		X (prior to procedure)						
24-Hour ABPM according to guidelines in Appendix L.7	X				X	X	X	X
EQ-5D and SF-36					X	X	X	X
Renal Denervation		X						

1 Month: 14 – 44 days 3 Months: 76-104 days - 6 Months: 166-194 days - 12 Months: 330-390 days - 24 Months: 690-750 days				**Post-Procedure** **(M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-24M visits)**				
Required Assessments	**Baseline**	**Renal Denervation**	**Prior to Discharge**	**1M**	**3M**	**6M**	**12M**	**24M**
Drug Testing	X				X	X	X	X
Renal Artery Imaging - Angiogram		X						
Renal Artery Imaging						X*	X****	X****
Mortality Assessment**				X	X	X	X	X
Medication Review, Event Review	All adverse events (AE) and medication review After 12 months, previously reported AEs will need to be reviewed and updated as needed							Serious AE and all medication review

* DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CT or angiogram to be used if DUS is non-diagnostic. Renal angiographyy must be used if repeat DUS/CTA/MRA is nondiagnostic or stenosis >60-70% is suspected.

** Conduct if follow-up visit missed

*** Bicarbonate will not be measured for subjects enrolled in Japan and Europe

**** DUS/CTA/MRA required as first line imaging modality at 12M (and 24M as applicable). Repeat DUS, MRA, or CTA to be used if prior imaging modality is nondiagnostic. If repeat DUS/CTA/MRA is nondiagnostic or evidence of a clinically significant stenosis (>60-70%) is indicated, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month without renal imaging will be required to undergo renal imaging at their next scheduled follow-up unless. For participating sites in Germany and the UK, only DUS or renal MRA imaging at the 12-month follow-up visit (or 24M follow-up as applicable) will be performed. For these countries, if the initial DUS or initial renal MRA is non-diagnostic, a repeat DUS or repeat renal MRA should be performed. If the initial imaging modality or subsequent repeat(s) are non-diagnostic, the investigator should choose the repeat imaging modality (DUS or MRA) that is expected to yield the required information for a diagnostic study.*****If not already collected at SV2

****** High-sensitivity CRP is not required to be measured for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed

Table 3: Schedule of Testing through 36 Months for Subjects with office SBP ≥180 mmHg (confirmed via 2 sets of measurements) or Escape via Investigator Discretion during Off-Medication Period Post-randomization

3 Months: 76-104 days- 6 Months: 166-194 days- 12 Months: 330-390 days - 24 Months: 690-750 days - 36 Months: 1050-1110 days		**Post-Procedure (Wk= ± 3 days, M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-36M visits)**									
Required Assessments	**Prior to Discharge**	**2Wk**	**4Wk**	**6Wk**	**8Wk**	**10Wk**	**3M**	**6M**	**12M**	**24M**	**36M**
Office Blood Pressure according to guidelines in Appendix L.7	X	X	X	X	X	X	X	X	X	X	X
Renal Artery Imaging								X[1]	X[3]	(X)[3]	(X)[3]
Mortality Assessment[2]		X	X	X	X	X	X	X	X	X	X
Medication Review, Event Review	All adverse events (AE) and medication review After 12 months, previously reported AEs will need to be reviewed and updated as needed									Serious AE and all medication review	

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.

2 Conduct if follow-up visit missed

3 DUS/CTA/MRA required as first line imaging modality at 12M (and 24M and 36M as applicable). Repeat DUS, MRA, or CTA to be used if prior imaging modality is nondiagnostic. If repeat DUS/CTA/MRA is nondiagnostic or evidence of a clinically significant stenosis (>60-70%) is indicated, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month without renal imaging will be required to undergo renal imaging at their next scheduled follow-up. For participating sites in Germany and the UK, only DUS or renal MRA imaging at the 12-month follow-up visit (or 24 or 36M follow-up as applicable) will be performed. For these countries, if the initial DUS or initial renal MRA is non-diagnostic, a repeat DUS or repeat renal MRA should be performed. If the initial imaging modality or subsequent repeat(s) are non-diagnostic, the investigator should choose the repeat imaging modality (DUS or MRA) that is expected to yield the required information for a diagnostic study.

B GENERAL INFORMATION

B.1 Introduction

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[1,2,3]. 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 in man 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, allowing for a single treatment in each renal artery and thus reduces the total procedure time compared to the single-electrode Symplicity renal denervation system. 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. With reduced procedure time, the patient is potentially exposed to less radiation and radiopaque contrast injections. 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.

B.1.1 Clinical Experience Using the Single Electrode RF renal denervation system

SYMPLICITY HTN-1 and SYMPLICITY HTN-2

Initial human studies of patients with resistant hypertension have demonstrated that the Symplicity™ renal denervation (RDN) system can safely denervate the kidney and that renal denervation has resulted in significant and sustained reductions of blood pressure out to three years[6,7]. SYMPLICITY HTN-1 utilized the Symplicity™ renal denervation system (which

included the single electrode catheter design) for treating patients with resistant hypertension. A total of 153 resistant hypertension patients with baseline office systolic blood pressure (SBP) ≥160 mmHg on ≥3 antihypertensive medications were treated. At the primary endpoint, 6 months post-denervation, the investigators reported a -22/-10 mmHg change in office SBP. Blood pressure reductions at 12, 24, and 36 months were -27/-14 mmHg, -29/-14 mmHg, and -32/-14 mmHg, respectively. There were no unanticipated adverse device effects or serious device-related or procedure-related complications. Through the 36-month follow-up, there were no late serious adverse events and no clinically significant changes in mean eGFR were reported[8].

The SYMPLICITY HTN-2 randomized, controlled study was conducted on a similar patient population as SYMPLICITY HTN-1 and the efficacy of RDN with the Symplicity™ catheter was compared with conventional medical therapy. Mean baseline blood pressure for the treatment group was 178/97 mmHg ± 18/16 mmHg; mean baseline blood pressure for the control group was 178/98 mmHg ± 16/17 mm Hg.

Ambulatory blood-pressure recordings were available for 20 patients in the renal denervation group, showing a mean decrease of 11/7 mm Hg (SD 15/11; p=0·006 for systolic blood pressure change, p=0·014 for diastolic blood pressure change) from baseline to 6 months, whereas averages did not change for 25 patients in the control group (−3/−1 mm Hg [19/12]; p=0·51 for systolic, p=0·75 for diastolic).

At the 6-month primary endpoint, the investigators reported a -32/-12 mmHg change in office SBP in the RDN group compared to a +1/0 change in the control group (p<0.0001).[9] At 24 months subjects in both RDN and cross-over groups had significant and sustained blood pressure reductions.

Thirty-six month results showed sustained lowering of office blood pressure at 3 years in subjects with severe, treatment-resistant hypertension without serious safety concerns. Blood pressure reduction at 36 months was -33/-14 mm Hg in the RDN group. In the Pooled RDN and crossover group, BP reduction at 30 months was -34/-13 mm Hg (n=69). Blood pressure reductions were achieved in absence of increases in blood pressure medications.

The safety profile for this study has been consistent with the SYMPLICITY HTN-1 study. In the SYMPLICITY HTN-2 population, there was one renal artery dissection from the injection of contrast into the renal artery wall during dye angiography; the lesion was stented without further consequences. One patient endured prolonged hospitalization in the crossover group due to hypotension following the RDN procedure. IV fluids were administered along with a decrease in antihypertensive medications and the patient was discharged without further incident. Other than these events with follow-up to 36 months, no other device-, procedure-, or therapy-related serious adverse events related to the delivery of radiofrequency energy to the renal artery with the Symplicity Flex™ catheter were reported. Importantly, the results of the SYMPLICITY HTN-2 study reaffirm the results of the SYMPLICITY HTN-1 study and showed a significant improvement in blood pressure reduction compared to optimal medical management in the control, without having a safety signal.

SYMPLICITY HTN-3

The SYMPLICITY HTN-3 Clinical Study was a multi-center, prospective, single-blind, randomized and controlled study that randomized 535 subjects in a 2:1 ratio to renal denervation plus best medical therapy vs. best medical therapy in the United States. The 6-

month SYMPLICITY HTN-3 clinical study results were presented at the 63rd Scientific Sessions of the American College of Cardiology (ACC) March, 2014 and published concurrently in the New England Journal of Medicine[10]. In office SBP, change (from baseline to 6-month follow-up) between the renal denervation arm and the control arm as the primary efficacy endpoint was a statistically non-significant difference of 2.39 mmHg [95% CI: -2.12 ~ 6.89, p=0.26], with a SBP reduction of 14.1 mmHg in the renal denervation arm vs. 11.7mmHg reduction in the control arm. The secondary endpoint was the comparison of SBP change (from baseline to 6 month follow-up) in mean 24-hour ambulatory blood pressure (ABP) between the renal denervation arm and the control arm using an automated ambulatory blood pressure monitor (ABPM). The result was a statistically non-significant difference of 1.96 mmHg, [95% CI, -1.06 to 4.97, p=0.98], with a SBP reduction of 6.8 mmHg in the renal denervation arm vs. 4.8 mmHg reduction in the control arm. The major explanation for the difference in efficacy findings between HTN-3 and the prior HTN-1 and HTN-2 studies was the inclusion of sham to the control arm.

The SYMPLICITY HTN-3 study met the primary safety endpoint, with a major adverse events rate of 1.4% (upper 95% confidence bound 2.9%) in the renal denervation arm, which was significantly (p<0.001) less than the pre-specified objective performance criterion of 9.8%. Twelve-month[11]data indicated there was no difference in major adverse events between the denervation and control groups. Subjects in the denervation group, control group that did not cross over, and control group subjects that crossed over at 6 months showed similar reductions in office and ambulatory blood pressure 12 months post-randomization.

Subjects randomized into SYMPLICITY HTN-3 were planned to be followed-up for 5 years post-procedure. However, it was decided to prematurely terminate the study after completion of 3-year follow-up visits for active subjects. Subjects had been allowed to cross-over from sham to treatment after the completion of the 6-month follow-up visit. In the overview below, the office blood pressure results for all treated subjects with the data available at the time of study closure is shown (Figure 1).

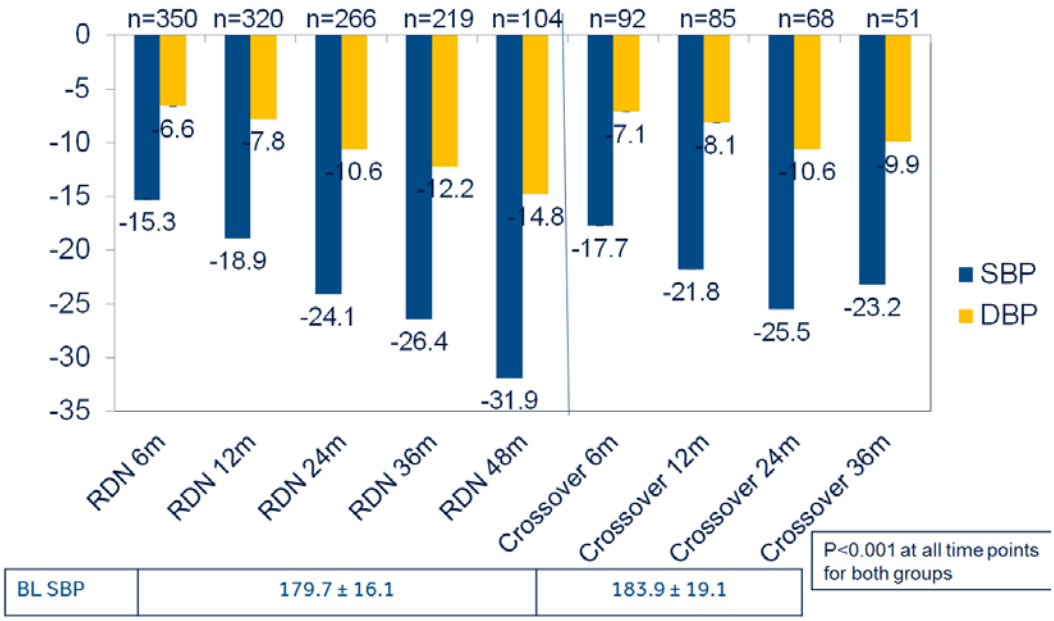

Figure 1: Change In Office Blood Pressure Through 36 And 48-Months Post-Randomization

***GLOBAL SYMPLICITY REGISTRY* (Conducted using Single electrode and multi electrodes RF renal denervation systems)**

The Global SYMPLICITY Registry is a prospective, multi-center, single-arm, non-interventional and open label registry that will collect descriptive data from a minimum of 3000 patients that receive renal denervation using the commercially available components of the Symplicity™ renal denervation system. Enrollment is ongoing in the Global SYMPLICITY Registry.

As of 04 October 2017, 2603 patients had been enrolled. The purpose of the registry is to document the long-term safety and effectiveness of renal denervation in a real-world patient population with hypertension. Of the 2515 subjects enrolled at the time of presentation at EuroPCR 2017, 2237 patients were treated with the Symplicity Flex™ catheter (Medtronic's first generation RDN catheter) and 278 with the Symplicity Spyral™ catheter. In the 849 Symplicity Flex™ subjects with 36-month follow-up data available, office blood pressure decreased on average by -16.5/-6.27 mmHg (p<0.001) from baseline to 36 months. In addition, 353 subjects had matched baseline and 6 months ambulatory blood pressure measurements (ABPM), although ABPM is not required in the GSR. In these subjects, the ambulatory systolic blood pressure reduction was -8.0 mmHg at 36 months.

The renal denervation procedure was associated with minimal complications and no unanticipated adverse device effects. Similar to SYMPLICITY HTN-1, HTN-2, and HTN-3, renal denervation did not elicit a significant change in measured renal function from baseline to 6 months.[12]

B.1.2 Clinical Experience Using the Multi Electrode RF renal denervation system (SPYRAL)

Multi-electrode RF Renal Denervation System Feasibility Study (Spyral FIM)

The SYMPLICITY Spyral FIM was a prospective, single-arm, non-randomized feasibility study to evaluate acute procedural and long term safety and effectiveness of the multi-electrode renal denervation system. Fifty (50) subjects were treated at four centers in Australia and New Zealand. Follow-up data through six months was presented at EuroPCR 2014[114]. The mean baseline office blood pressure was 181/95 ± 17/12 mmHg and patients were taking an average of 4.6 ± 1.3 antihypertensive medications. Mean baseline ambulatory systolic and diastolic BP were 154.4 ± 17.4 mm Hg and 80.9 ± 11.7 mm Hg during 24-hour ABPM, respectively. There was a reduction in 24-hour ambulatory blood pressure measurement at 6 months with a change in systolic blood pressure of -5.7 mmHg and a change in diastolic of -4.5 mmHg. At 12 months, the difference in systolic ambulatory blood pressure from baseline was -7.5 mmHg and the difference in diastolic was -6.0 mmHg. The mean systolic ambulatory blood pressure change from baseline was decreased by 7.6 mmHg at the 36 month visit.

At six months post treatment, there was a -20/-7 mmHg change in office blood pressure (Figure 2) and subjects were on an average of 4.8 ± 1.1 antihypertensive medications. Sixty-six percent of patients had an office SBP reduction of at least 10 mmHg at 6 months. Follow-up data through 12 months were published in EuroIntervention in May 2015[40]. The mean change of office systolic blood pressure at 36 months from baseline was -20.8 ± 28.6 mmHg.

Twenty-eight out of 41 (68.3%) of the subjects achieved a reduction in systolic BP of ≥ 10 mm Hg while 53.7%(22/41) had a systolic BP reduction of ≥ 20 mm Hg.

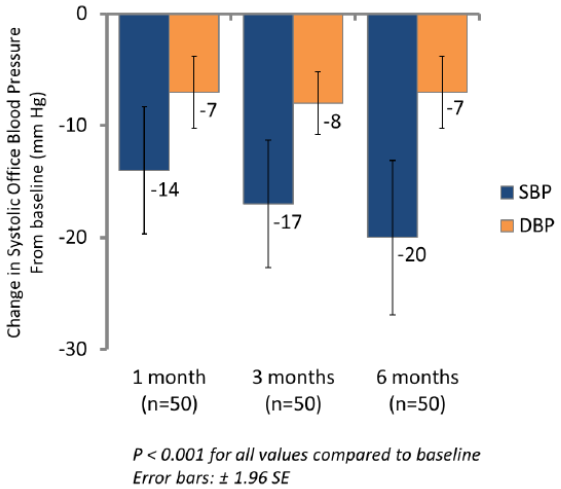

Figure 2: Change In Office Blood Pressure From Baseline Through 6 Months

There were no unanticipated adverse device effects. Three subjects developed a pseudoaneurysm at the femoral access site and two of these subjects also reported a hematoma. All five access site related events were treated without any subsequent complication. Follow-up renal artery imaging (duplex ultrasound) was performed at six months post treatment, with no reports of renal artery stenosis. One subject had a myocardial infarction (MI) one month after renal denervation treatment. The subject underwent a percutaneous coronary intervention (PCI) and was stented. The MI event was reviewed and determined to be unrelated to the device, therapy, or procedure by the Clinical Events Committee.

The change in Serum Creatinine at 36 months was 0.1 ± 0.2 (p=0.014 for change from baseline). The change in eGFR at 36 months was -6.7 ± 16.6 (p=0.013 for change from baseline). There were 2 cardiovascular deaths (4.3%), 3 subjects with MI (6.5%), 3 subjects with serum creatinine elevation > 50% (6.5%), 3 subjects with vascular complications (6.5%), and 2 subjects with stroke (4.3%). These are all at levels that are expected in a patient population of severe drug resistant hypertension.

The Symplicity Spyral™ catheter and Symplicity G3™ generator had a sustained safety profile at 36 months with 2 deaths described above, no new hypertensive crises and no end stage renal disease at the time of the 36 month data analysis. The 2 deaths were adjudicated by the CEC as not related to the device, therapy or procedure. One subject died from a subarachnoid hemorrhage while the other subject died from an intracranial hemorrhage.

SPYRAL COHORT OF THE GLOBAL SYMPLICITY REGISTRY (GSR)

An addendum to the GSR allowed use of the Symplicity Spyral catheter and Symplicity G3 generator following CE mark approval in Europe. In addition to the general registry, a sub-study of patients treated with the Spyral catheter is being enrolled. This registry sub-study will be 100% monitored for increased data quality. The recommended follow-up for these patients is 3, 6, and 12 months and then annually for a minimum of 3 years and up to 5 years. Data

from 278 subjects in the Spyral sub-study was presented at EuroPCR 2017 with data out to two years for 108 subjects. Subjects presented with a mean ambulatory systolic blood pressure of 157 ± 18mm Hg and a mean baseline office systolic blood pressure of 171 ± 23 mmHg.

Ambulatory SBP showed sustained reductions to two years with a mean decrease of 10.4 mmHg. Sustained reductions in office SBP were also reported to two years with a mean reduction of 12 mmHg. These data demonstrate that renal denervation in this real world population resulted in significant reductions in both ambulatory and office blood pressure that were sustained out to 2 years post-procedure with a very low rate of safety events.

Safety results from the Spyral sub-study of the GSR to 24 months continue to support the safety profile of the Symplicity Spyral™ catheter.

SPYRAL HTN-OFF MED 80 PATIENT COHORT

SPYRAL HTN-OFF MED is a multicenter, international, single-blind, randomized, sham-controlled trial. Eligible patients are drug-naive or discontinue their antihypertensive medications. Patients with an office systolic blood pressure (SBP) of 150 mm Hg or greater and less than 180 mm Hg, office diastolic blood pressure (DBP) of 90 mm Hg or greater, and a mean 24-h ambulatory SBP of 140 mm Hg or greater and less than 170 mm Hg at second screening, have renal angiography and are randomly assigned to renal denervation or sham control. Patients, caregivers, and those assessing blood pressure are blinded to randomization assignments.

While study enrollment is ongoing, data from the initial 80 patients with 3 months follow up from the SPYRAL HTN-OFF MED study was presented at ESC Congress in August 2017. Concurrently, an article presenting the data was published in the Lancet. A brief summary of the SPYRAL HTN-OFF MED data is provided below.

The primary endpoint, change in 24-h blood pressure at 3 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 at 3 months.

Between June 25, 2015, and January 30, 2017, 353 patients were screened. 80 patients were randomly assigned to renal denervation (n=38) or sham control (n=42) and followed up for 3 months at 21 centers in the USA, Europe, Japan, and Australia.

There were no major adverse events in either group. No major procedural or clinical safety events were observed in either the renal denervation or sham control groups throughout the 3 months. Specifically, there were no deaths or occurrences of myocardial infarction, stroke, major bleeding, serum creatinine elevation greater than 50%, significant embolic events, vascular complications, renal artery re-intervention, new or worsening renal failure, or hypertensive emergency or crisis.

Office and 24-h ambulatory blood pressure decreased significantly from baseline to 3 months in the renal denervation group (Figure 3). No significant changes were seen in the sham-

control group. 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.

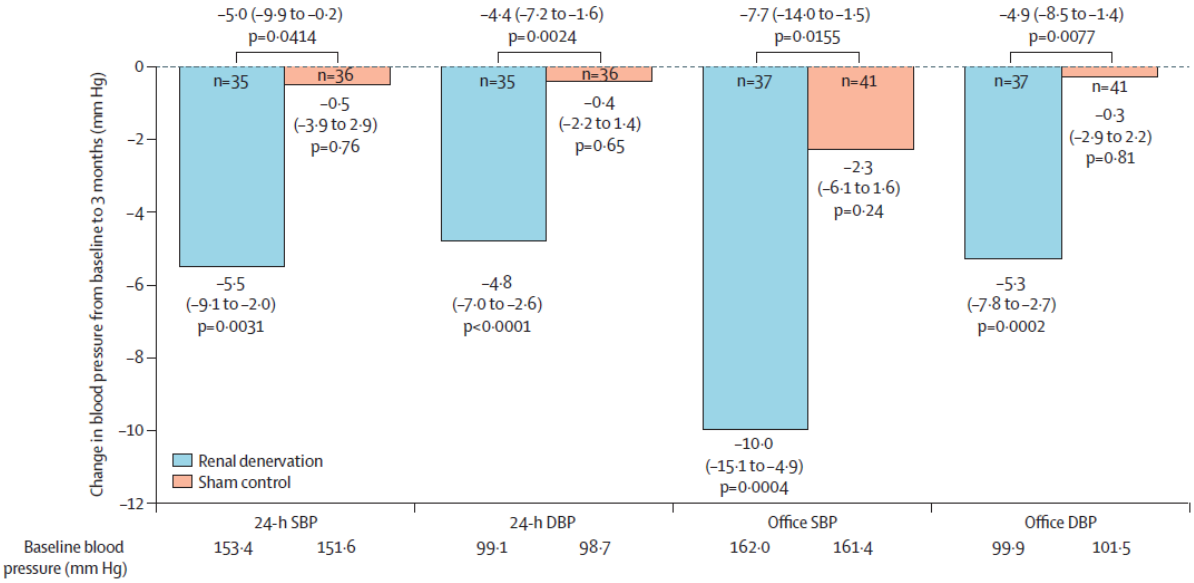

Figure 3: Changes At 3 Months In Office And Ambulatory Sbp And Dbp For Renal Denervation And Sham Control Groups

These initial results from SPYRAL HTN-OFF MED provide biological proof of principle for the blood-pressure-lowering efficacy of renal denervation. The data indicates that denervation is safe with no major adverse events to 3 months. This data will be utilized as the informative prior dataset for the SPYRAL PIVOTAL - SPYRAL HTN-OFF MED, which is a continuation of the current SPYRAL HTN-OFF MED study.

SPYRAL Pivotal - SPYRAL HTN-OFF MED First Interim Analysis

The SPYRAL PIVOTAL - SPYRAL HTN-OFF MED study is a multi-center, international, prospective, single blinded, randomized, interventional, sham-controlled study. In order to test the hypothesis that renal denervation decreases blood pressure and is safe when studied in the absence of antihypertensive medications, study subjects will be 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 will also be blinded to study subjects' randomization assignment through the primary endpoint to prevent potential bias of results. Subjects will be 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 intetim analysis in February 2020. Data from the initial 80 patients with 3 months follow up from the SPYRAL HTN-OFF MED study was combined with data from the initial 251 patients with 3 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 3 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 3 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 1 month. There was one major safety event in each treatment group up to 3 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 3 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 3-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 analysed using the prespecified ANCOVA-adjusted frequentist analysis of the overall population show similar changes in blood pressure to Bayesian results (Figure 4).

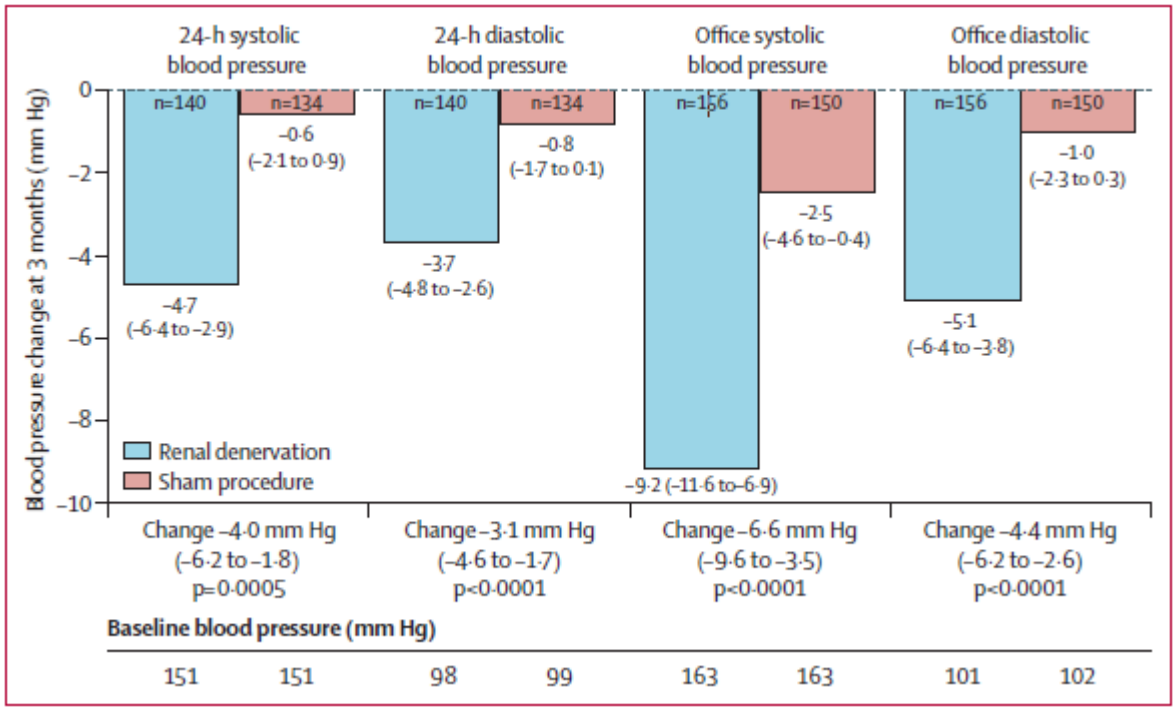

Figure 4: Changes in 24-h and office systolic and diastolic blood pressure from baseline to 3 months

SPYRAL HTN-ON MED 80-PATIENT COHORT

SPYRAL HTN-ON MED is a multicenter, international, single-blind, randomized, sham-controlled trial. Eligible patients are on a stable dose of one to three antihypertensive medications for at least 6 weeks. Patients with an office systolic blood pressure (SBP) of 150 mm Hg or greater and less than 180 mm Hg, office diastolic blood pressure (DBP) of 90 mm Hg or greater, and a mean 24-h ambulatory SBP of 140 mm Hg or greater and less than 170 mm Hg at second screening, have renal angiography and are randomly assigned to renal denervation or sham control. Patients, caregivers, and those assessing blood pressure are blinded to randomization assignments.

While study enrollment is ongoing, data from the initial 80 patients with 6 months follow up from the SPYRAL HTN-ON MED study was presented at ESC Congress in May 2018. Concurrently, an article presenting the data was published in The Lancet42. A summary of the SPYRAL HTN-ON MED data is provided below.

The primary endpoint, change in 24-h blood pressure at 6 months, was compared between randomization groups. Drug surveillance was done to ensure patient compliance with absence of their prescribed antihypertensive medication. The primary analysis was done in the intention-to-treat population. Safety events were assessed at 6 months.

Between June 22, 2015, and June 14, 2017, 467 patients were screened. 80 patients were randomly assigned to renal denervation (n=38) or sham control (n=42) and followed up for 6 months at 25 centers in the USA, Europe, Japan, and Australia.

There were no major adverse events in either group. No major procedural or clinical safety events were observed in either the renal denervation or sham control groups throughout the 6 months. Specifically, there were no deaths or occurrences of myocardial infarction, stroke, major bleeding, serum creatinine elevation greater than 50%, significant embolic events, vascular complications, renal artery re-intervention, new or worsening renal failure, or hypertensive emergency or crisis.

Office and 24-hour ambulatory blood pressure decreased significantly from baseline to 6 months in the renal denervation group (Figure 5). No significant changes were seen in the sham-control group. The mean difference between the groups favored renal denervation for 6-months change in both office and 24-h blood pressure from baseline: 24-h SBP –7·4 mm Hg (95% CI –12.5 to –2.3; p=0·0051), 24-h DBP –4·1 mm Hg (–7·8 to –0.4; p=0·0292), office SBP –6.8 mm Hg (–12.5 to –1.1; p=0·0205), and office DBP –3.5 mm Hg (–7.0 to –0; p=0·0478). Baseline-adjusted analyses showed similar findings.

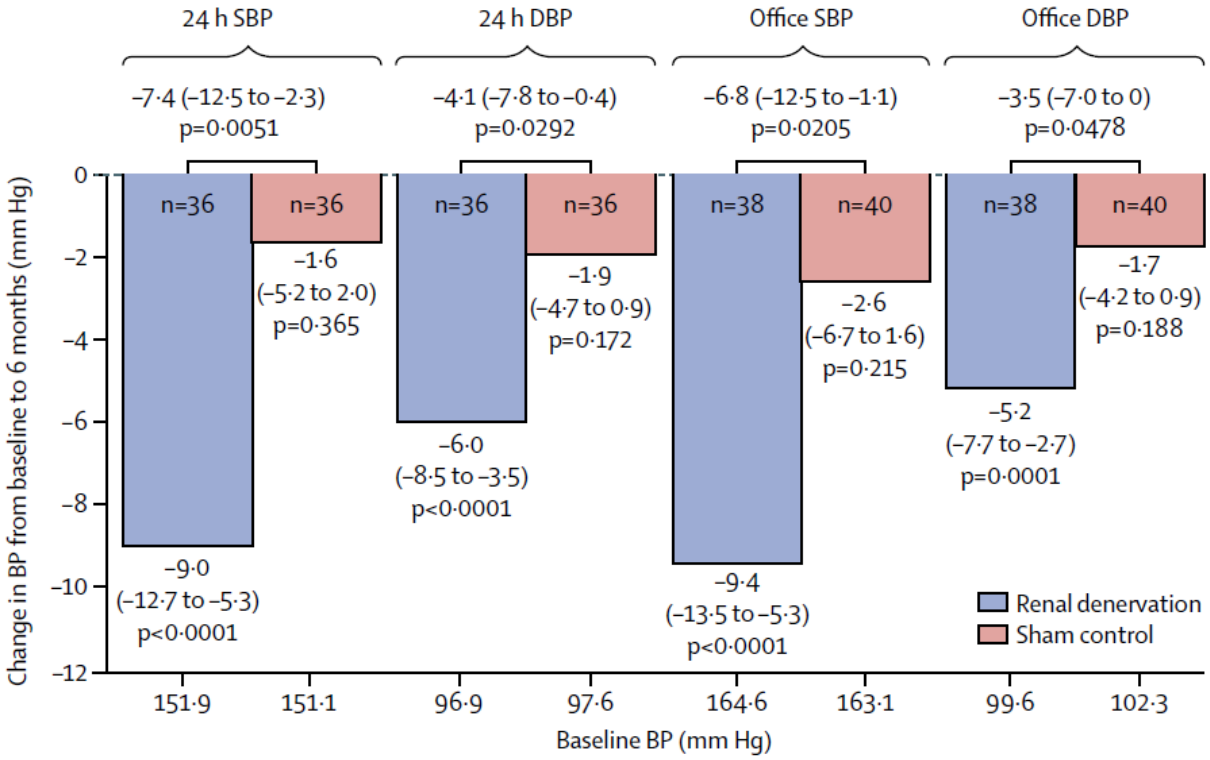

Figure 5: Changes at 6 Months in Office and Ambulatory SBP and DBP for Renal Denervation and Sham Control Groups

These initial results from SPYRAL HTN-ON MED in combination with SPYRAL HTN-OFF MED demonstrated biological proof of principle for the blood-pressure-lowering efficacy of renal denervation. The data indicates that renal denervation is safe with no major adverse events at 3 and 6 months. The SPYRAL HTN-ON MED data will be utilized as the informative prior dataset for the continuation of the current SPYRAL HTN-ON MED study.

Clinical Summary and Future Studies

Extensive data has been collected on the predicate of the Symplicity Spyral™ catheter, the single-electrode Symplicity™ catheter. This includes data from the SYMPLICITY HTN-1 study (36 months), the SYMPLICITY HTN-2 study (36 months), as well as the data from the SYMPLICITY HTN-3 Study (36 months) and the Global SYMPLICITY Registry.

The data from the Spyral FIM study using the multi-electrode renal denervation system supports the procedural and acute safety of this device in treating subjects with uncontrolled hypertension. Six months post-procedure there was a significant reduction in office BP compared to baseline. This reduction continued through 36 months follow-up. Safety events reflect those commonly seen with arterial access and none related to the renal denervation device or treatment were reported.

The combined experience from these studies in over 4206 subjects enrolled to date indicates that use of the Symplicity™ renal denervation system to denervate the kidneys is safe. In contrast to findings from earlier studies, patients treated with RDN in SYMPLICITY HTN-3 did not have a significant reduction in office and ambulatory BP at 6 months compared to the control group, and the primary efficacy endpoint was not met. Possible confounding factors such as inadequate denervation during the procedure, the target patient population studied, and uncontrolled medication adherence are believed to have impacted the SYMPLICITY HTN-3 results. The aims of this study is to demonstrate the acute procedural safety, document the effect of renal denervation on blood pressure control with simultaneous RF energy delivery at multiple sites using Medtronic's next generation Symplicity Spyral™ catheter and address the confounding factors observed in SYMPLICITY HTN-3.

The SPYRAL FIM, GSR Spyral sub-study, and SPYRAL HTN-OFF MED Feasibility study include 388 patients and demonstrate safety and efficacy of the Spyral renal denervation system in resistant hypertensive, real-world, and off med populations, respectively. Specifically, results from the SPYRAL HTN-OFF MED trial provide biological proof of principle for the efficacy of catheter-based renal denervation to reduce blood pressure in patients with hypertension not treated with antihypertensive medications. The study demonstrated a clinically significant reduction in office and 24-h ambulatory SBP and DBP at 3 months in patients with mild to moderate hypertension following renal denervation in the absence of antihypertensive medications that was not observed in the sham control group. There were no major safety events in either group despite the absence of pharmacological therapy from enrolment to the 3-month follow-up and a more aggressive renal denervation procedure than that of previous trials in this setting, extending into renal artery branch vessels.

B.2 Device information

B.2.1 The Symplicity™ multi-electrode renal denervation system

The Symplicity™ 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 outside the United States, Canada, and Japan.

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

B.2.2 Symplicity Spyral™ Catheter

The Symplicity Spyral™ catheter is an iteration of the single-electrode Symplicity™ catheter and 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 6). 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 7). 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 6: 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.

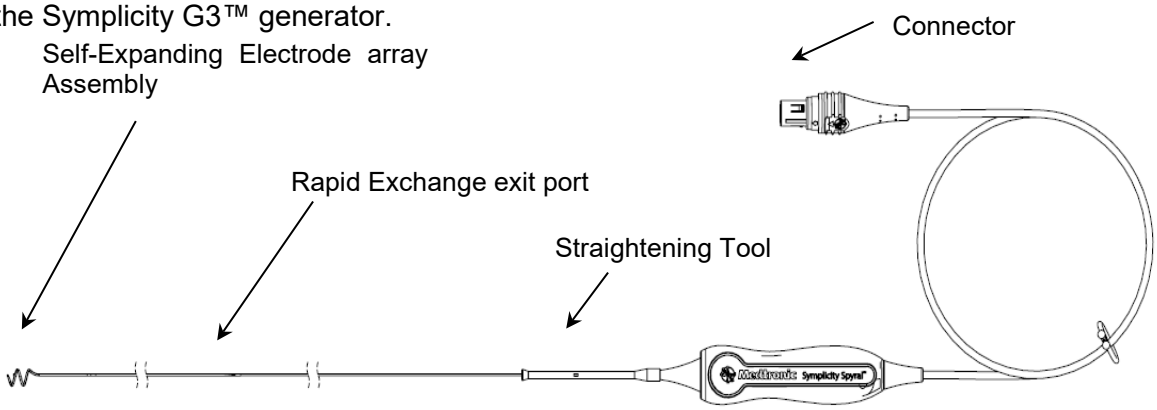

Figure 7: Overview of Symplicity Spyral™ Catheter

Unlike the single-electrode Symplicity™ catheter, which had to be rotated to treat different segments of the vessel, 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.

B.2.3 Symplicity G3™ Generator

The Symplicity G3™ generator is an iteration of the existing Symplicity™ generator and is intended to provide a safe and effective means of delivering RF energy to the Symplicity Spyral™ and Symplicity™ catheters 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 previous 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
    - ***Note:*** In Japan, the RFID module will be turned off
- 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 8: Symplicity G3™ Generator

The Symplicity Spyral™ catheter leverages the safety aspects of the original algorithm while incorporating new features to allow for a shorter treatment time. 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. As with the previous generator the 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. Similar to the previous

generation SymplicityTM generator, temperature and impedance values are monitored at each electrode and used to provide input to an algorithm controlling power delivery for individual electrodes (Figure 9).

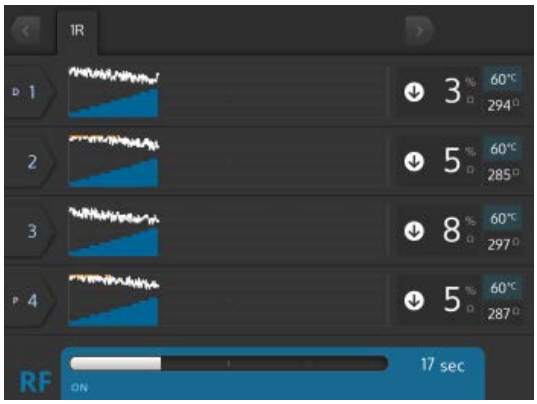

Figure 9: RF on Screen

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

B.2.4 Labeling

The Symplicity Spyral™ catheter and Symplicity G3™ generator will include, but not limited to, 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 the sponsor

In geographies, where the product is not commercially approved, labeling will be provided according to geography requirements.

An Instructions for Use document is included with each Symplicity Spyral™ catheter and a User's Manual is included with each Symplicity G3™ generator.

B.2.5 Intended Clinical Performance

In the past, surgical nephrectomy, and even radical surgical sympathectomy, were both used to treat severe hypertension. Importantly, a denervated kidney maintains appropriate electrolyte and volume homeostasis as demonstrated in the human transplant experience. The Symplicity Spyral™ catheter offers a significantly less-invasive approach to treating hypertension - a straightforward, catheter-based procedure with four electrodes spatially distributed along a spiral simultaneously delivering radiofrequency energy to shorten procedure time.

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 8) without adversely affecting the wall of the artery or surrounding organs.

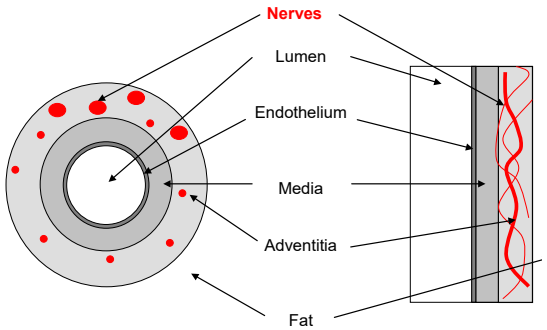

Figure 10: Illustration of renal artery anatomy

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 ability to denervate using this approach has been demonstrated to effectively reduce renal nerve activity.

Recent preclinical studies and histological analyses [15-17] observed that renal nerves may have a positional bias, suggesting the distal nerves are closer to the arterial lumen (Figure 11). 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.

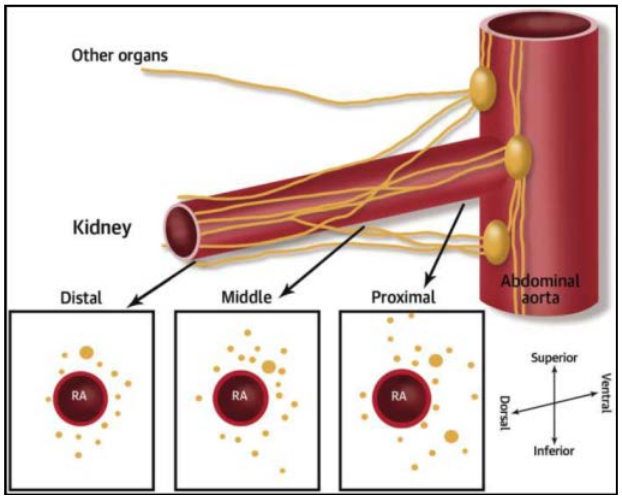

Figure 11: Illustration Of Peri-Arterial Renal Nerve Location

Initial clinical evidence[18,19]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. Utilization of the branch and main renal artery treatment approach will be evaluated in this SPYRAL PIVOTAL - SPYRAL HTN-OFF MED clinical study to confirm the safety and efficacy of this approach.

B.3 Comparator information

A review of hypertension studies of antihypertensive medications was undertaken in concert 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 3-4 week washout period free of antihypertensive medications followed by a 12 week post-procedure comparison of the investigational therapy (Denervation group) to a group receiving the sham procedure (Control group). 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 of a sham procedure in the control group will help “blind” the subject to their randomization group.

Inclusion and Exclusion criteria traditionally used in pharmaceutical studies[20] will be utilized as they have historically ensured that only patients with true hypertension (vs white coat) are included and also ensure that these patients are not borderline hypertensive (ABP 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.

C STUDY PLAN

C.1 Study Objective

The objective of this study is to test the hypothesis that renal denervation decreases blood pressure and is safe when studied in the absence of antihypertensive medications. In this study, "uncontrolled hypertension" is defined as an office systolic blood pressure (SBP) ≥ 150 mmHg and <180 mmHg, an office DBP ≥90 mmHg and a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) average SBP ≥140 mmHg to <170 mmHg, all of which are measured at Screening Visit 2 (per Appendix L7).

Data obtained without the presence of antihypertensive medications will be used to confirm the effect of renal denervation on elevated blood pressure.

The data collected in this study will be used to support regulatory submissions around the world to obtain market approval for the Symplicity Spyral™ multi-electrode renal denervation catheter (Symplicity Spyral™ catheter) and the Symplicity G3™ renal denervation RF generator, from regulatory entities, including, but not limited to: the Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, and the U.S. Food and Drug Administration (FDA).

C.2 Clinical Endpoints

Primary Endpoints

There are two primary endpoints in this study (one safety and one efficacy). The study will be considered successful if both the primary safety and efficacy endpoint hypotheses are met

Powered Primary Safety Endpoint

- Incidence of Major Adverse Events (MAE), defined as a composite of the following events, through one month post-randomization (6 months for new renal artery stenosis)
  - 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 laboratory

Powered Primary Efficacy Endpoint

- Baseline adjusted change (using Analysis of Covariance) in systolic blood pressure (SBP) from baseline (Screening Visit 2) to 3 months post-procedure as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM).

Secondary Endpoints

Powered Secondary Efficacy Endpoint

- Baseline adjusted change (using Analysis of Covariance) in office systolic blood pressure from baseline (Screening Visit 2) to 3 months post-procedure.

Secondary Safety Endpoints

- Acute/Procedural Safety Secondary Endpoints – Compared Between Groups at 1 Month Post-Procedure:
  - Significant embolic event resulting in end-organ damage
  - Renal artery perforation requiring intervention
  - Renal artery dissection requiring intervention
  - Vascular complications
  - End-Stage Renal Disease
  - ≥40% decline in eGFR
  - New Myocardial Infarction
  - New Stroke
  - Renal artery re-intervention
  - Major bleeding according to TIMI definition (i.e. intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)
  - Increase in serum creatinine > 50% from Screening Visit 2
  - New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core laboratory
  - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol.
- Chronic Safety Secondary Endpoints – Compared Between Groups at 3, 6, 12, 24, and 36 Months Post- Randomization:
  - All-cause mortality
  - End-Stage Renal Disease
  - ≥40% decline in eGFR
  - New Myocardial Infarction
  - New Stroke

- Renal artery re-intervention
- Major bleeding according to TIMI definition (i.e. intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)
- Increase in serum creatinine > 50% from Screening Visit 2
- New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core laboratory
- Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol.

- Secondary Efficacy Endpoints – Compared Between Groups
  - Change in systolic blood pressure (SBP) from baseline (Screening Visit 2) as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM) at 3, 6, 12, 24 and 36 months post-procedure.
  - Change in office systolic blood pressure from baseline (Screening Visit 2) at 1, 3, 6, 12, 24 and 36 months post-procedure.
  - Incidence of achieving target office systolic blood pressure (SBP <140 mmHg) at 1, 3, 6, 12, 24 and 36 months post-procedure.
  - Change in office diastolic blood pressure from baseline (Screening Visit 2) at 1, 3, 6, 12, 24 and 36 months post-procedure.
  - Change in diastolic blood pressure from baseline (Screening Visit 2) as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM) at 3, 6, 12, 24 and 36 months post-procedure.
- Summary of Quality of Life (QOL) Measures (EQ5D and SF36)

C.2.1 Additional analyses

The following additional analysis will be conducted:

- Antihypertensive medication usage throughout the study, including escape subjects prior to 3-months and subjects reintroduced to medications after 3 months
- Additional procedural characteristics e.g. treatment duration, frequency of distal renal artery treatment, ablations per vessel, location of ablations, number of ablations per patient and other characteristics will be analyzed to assess their impact on blood pressure.

C.3 Study Population

This study will randomize subjects who meet the criteria as detailed in the Subject Selection portion of this Clinical Investigation Plan. Potentially eligible subjects will be consented and entered into a screening period to cease all antihypertensive medications and establish a baseline 24-hour ABPM and office systolic blood pressure. Approximately 433 subjects (including the first consecutively randomized 80 subjects in the SPYRAL HTN-OFF MED study) will be allowed to be randomized.

Eligible subjects will be randomized at a 1:1 ratio to:

- Denervation group: Subjects are treated with the renal denervation procedure after randomization.
- Control group: Subjects undergo a sham renal denervation procedure.

C.4 Study Design

The SPYRAL PIVOTAL - SPYRAL HTN-OFF MED study is a multi-center, international, prospective, single blinded, randomized, interventional, sham-controlled study. In order to test the hypothesis that renal denervation decreases blood pressure and is safe when studied in the absence of antihypertensive medications, study subjects will be 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 will also be blinded to study subjects' randomization assignment through the primary endpoint to prevent potential bias of results. See section C.5 for blinding techniques. Subjects will be studied in the absence of antihypertensive medications to assess the impact of renal denervation on systolic blood pressure in the absence of medication.

The Symplicity Spyral™ catheter and Symplicity G3™ generator provide a spiral pattern of denervation, ensuring circumferential nerve ablation that is expected to minimize procedure variability. One Symplicity G3™ generator is used with a Symplicity Spyral™ catheter in subjects randomized to the denervation group, or if applicable, in control subjects eligible for cross-over.

It is anticipated that several subjects will no longer meet study eligibility after the medication washout period, renal artery imaging, or measurement of OBP, ABPM, and renal function. Approximately 1800 patients will be enrolled to randomize approximately 433 subjects (including the first 80 consecutively randomized to the SPYRAL HTN-OFF MED study) in the study.

C.5 Randomization and blinding

Randomization will be stratified by study center at a 1:1 ratio to:

- Denervation group: Subjects remain blinded and are treated with the renal denervation procedure.
- Control group: Subjects remain blinded and remain on the catheterization lab table for at least 20 minutes prior to introducer sheath removal.

Investigational sites will access randomization allocation via a password-protected system that can only be accessed by those approved by the study sponsor.

All study staff and necessary hospital personnel will be instructed that subjects are not to be informed of their randomization assignments and appropriate measures should be taken to minimize the risk of premature unblinding.

The Investigator performing the catheterization lab procedures and his/her designated study staff will be blinded to a subject's randomization group up until the angiography is completed and inclusion/exclusion confirmed. However, investigators performing study follow-up visits

and the subject's referring/managing physicians will not be proactively informed of a subject's treatment assignment to minimize potential bias in the subject's care decisions. However, to specifically minimize potential bias in the measurement of Office BP and ABPM, each investigational site will specify several designated "blinded" members of their study staff that will not be informed of the subject's group assignments and will be responsible for performing the office blood pressure measurements, conducting ABPM preparation and printing results upon a patient completing the ABPM. Prior to unblinding, the blinding effectiveness will be assessed by asking blinded study staff which group they believe the subject was randomized to.

Subjects will be blinded during the renal angiogram by a combination of conscious sedation, sensory isolation (e.g., blindfold and music), and lack of familiarity to the procedural details and duration (i.e., subjects will not know the difference between the renal angiography procedure alone and the renal angiography and denervation procedure). Subjects will continue to be blinded by only interacting with blinded site personnel through the 6 month follow-up visit post-procedure. Blinding effectiveness will be assessed by asking the subject which group they believe they were randomized to. All subjects will be unblinded after the completion of their required 6-month follow-up testing.

If the subject's medical condition requires knowledge of the randomization group in order to provide adequate care, prior to unblinding, contact the study sponsor with the justification for proposed unblinding.

C.6 Sample Size

This study will be conducted as an adaptive Bayesian trial with an informative prior. A Bayesian power prior approach[38,39] in conjunction with a discount function will be used to incorporate the historical data. The discount function reduces the strength of the historical data if disagreements are observed with the current data.

The prior data consists of the first consecutively randomized 80 subjects in the SPYRAL HTN-OFF MED study. The weight of the prior data will be adjusted using a discount function, which scales from 0 to 1, according to the similarity of the prior and pivotal data. This discount function adjusts the amount of weight the prior receives. This prevents the use of an informative prior where exchangeability issues are present (e.g., the prior and pivotal data are quite different). This discount function approach was proposed by the Medical Device Innovative Consortium (MDIC) working group and is a collaborative effort between FDA and industry through the MDIC[36,37] If the analyses show a high level of agreement for pivotal data compared to the prior, the prior will be weighted at or near 100%. If the pivotal data perform worse than or much better than the prior, then the prior will receive very little or zero weight. The Bayesian adaptive design is set up to enroll patients until a sufficient sample size is achieved to have high probability of meeting the endpoint.

The sample size will vary from 210 to 300 (not including the first consecutively randomized 80 patients) subjects due to the adaptive nature of the trial. This will require randomizing approximately 247 to 353 subjects to account for an expected 15% attrition at 3-months. The interim analyses will take place when N=210 and N=240 subjects have 3-month follow-up data visit, with a maximum study size of 300 subjects if the study does not stop at either interim look. The SPYRAL PIVOTAL - SPYRAL HTN-OFF MED study will thus in total randomize approximately 433 subjects (including the first consecutively randomized 80 subjects) . Interim analyses will be conducted and reviewed by the DSMB, along with an independent

organization that will be performing the Bayesian analyses. Medtronic personnel will not have access to any unblinded results prior to the primary endpoint analyses. At each interim analysis, enrollment may be stopped for futility or efficacy. Both the primary and secondary effectiveness endpoints will be evaluated during these interim looks and enrollment will only stop at an interim analysis if both endpoints meet the following stopping criteria.

1. The first interim analysis takes place when the first 210 subjects have 3-month follow-up data available (requiring approximately 247 randomized subjects to account for attrition). The Bayesian efficacy analysis will be performed and P[suc] will be calculated, where P[suc] is the probability of accepting the alternative efficacy endpoint hypotheses, $P(\mu < 0 | y, y_0, \widehat{\alpha_0}(y, y_0, \lambda, k))$, , and is defined in detail in section H4.
    a. If P[suc] > 0.975 for both the primary and secondary efficacy endpoints, then the study has met the efficacy hypotheses and enrollment will be stopped. Any additional subjects that have been enrolled before the decision is made to stop for efficacy will be pooled with the existing subjects and analyzed as a secondary cohort.
    b. We calculate the probability of futility based on the maximum study size of 300 evaluable subjects which requires us to impute the outcomes for subjects who have not yet been enrolled. If the posterior probability of futility from this calculation is < 0.05 for both the primary and secondary efficacy endpoints, then the study will have met the futility boundary and enrollment will be stopped.. Further details can be found in the study SAP. Any additional subjects that have been enrolled before the decision is made to stop for futility will be pooled with the existing subjects and analyzed as a secondary cohort.
    c. If P[suc] is ≥0.05 and ≤0.975 for either the primary or secondary efficacy endpoints, then subject enrollment will continueto the second interim analysis.
2. If the study doesn't stop for efficacy or futility at the first interim analysis then enrollment will continue until the second interim analysis when 3-month follow-up data is available for the first 240 subjects (requiring approximately 282 randomized subjects to account for attrition). The Bayesian efficacy analysis will be performed and P[suc] will be calculated.
    a. If P[suc] > 0.975 for both the primary and secondary efficacy endpoints, then the study has met the efficacy hypotheses and enrollment will be stopped. Any additional subjects that have been enrolled before the decision is made to stop for efficacy will be pooled with the existing subjects and analyzed as a secondary cohort.
    b. We calculate the probability of futility based on the maximum study size of 300 evaluable subjects which requires us to impute the outcomes for subjects who have not yet been enrolled. If the posterior probability of futility from this calculation is < 0.05 for both the primary and secondary efficacy endpoints, then the study will have met the futility boundary and enrollment will be stopped. Further details can be found in the study SAP. Any additional subjects that have been enrolled before the decision is made to stop for futility will be pooled with the existing subjects and analyzed as a secondary cohort.
    c. If P[suc] is ≥0.05 and ≤0.975 for either the primary or secondary efficacy endpoints, then we continue enrolling subjects to the final analysis.

3. If the study doesn't stop for efficacy or futility at the second interim analysis then enrollment will continue until the maximum study size of 300 subjects with 3-month follow-up data (requiring approximately 353 randomized subjects to account for attrition). The Bayesian efficacy analysis will be performed and P[suc] will be calculated.
    a. If P[suc] > 0.975 for the primary efficacy endpoint, then we have met the primary efficacy hypothesis.
    b. If P[suc] > 0.975 for the secondary efficacy endpoint, then we have met the secondary efficacy hypothesis.

C.7 Number of investigation sites and study duration

The study is expected to be conducted in up to 50 sites located around the world. A multi-site, multi-national design helps to ensure a representative sample of the global population as well as maintaining a reasonable enrollment duration. Participating geographies may include countries such as the United States, Japan, Australia, Canada, and countries where CE mark applies. A list of participating investigational sites including Investigators' names who are responsible for conducting the trial, their title, address, and telephone number(s) are provided separately and will be maintained within the study files at each site. Additional geographies may be added to the clinical study at a later date and the approval status will be documented under a separate cover. Enrollment to the prospective cohort is expected to take approximately 33 months. Individual investigational sites may randomize up to 20% of the total study subjects. At least 50% of randomized subjects, excluding the first consecutively-randomized 80 subjects, must be randomized from sites in North America (US and Canada). Subjects will participate in the study from the time of signing consent until study exit or the time of completion of 3 years of follow-up post-procedure. Control (sham) subjects will be followed-up for two years post-procedure, if they (and their study doctor) agree to have the renal denervation procedure after their 6 month follow-up, "crossover".

If a site does not enroll any subjects into the study within three months of activation, they may forfeit their participation in the clinical study to another site to ensure timely enrollment.

D SUBJECT SELECTION

D.1 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 a diastolic blood pressure (DBP) ≥90 mmHg at Screening Visit 2, according to guidelines in Appendix L.7.

3. Individual has a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) average SBP ≥140 mmHg and <170 mmHg at Screening Visit 2 according to guidelines in Appendix L.7: ABPM is considered valid if the number of successful daytime readings captured is ≥ 21 and the number of successful nighttime readings captured is ≥ 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 three month post-procedure visit.

D.2 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 renal artery anatomy that is ineligible for treatment including:
    a. Main renal artery for each kidney less than 3mm or greater than 8mm
    b. Lacks a main renal arterial vessel (greater than 3mm and less than 8mm in diameter) for each kidney that does not allow 4 simultaneous quadrantic (4SQ) radio frequency ablations in the main renal artery or equivalent (defined as 4SQ ablations in all branch vessels greater than 3mm and less than 8mm)
4. Presence of FMD (defined as visible beading of the artery on angiography)
5. Has >50% stenosis in any treatable vessel
6. Has a renal artery stent placed <3 months prior to the denervation procedure
7. Presence of an aneurysm defined as any localized increase in the diameter of the vessel
8. Treatment area within 5mm of a segment in the renal artery which contains any of the following:
    a. Atheroma,
    b. Calcification, or
    c. Renal artery stent

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 patient is black) x 0.742 (if female). (NOTE: an eGFR calculation specific to Japanese patients will be used for subjects enrolled in Japan)
10. Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%.
11. Individual is taking SGLT2 inhibitors or GLP-1 agonists that have been prescribed < 90 days from Screening Visit 1 or who does not plan to remain 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 reduction of SBP of ≥20 mmHg or DBP of ≥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 who requires more than occasional use (e.g. PRN) of narcotic drugs over the month prior to Screening Visit 1.

15. Individual has documented primary pulmonary hypertension.
16. Individual has an untreated secondary cause of hypertension (either known or suspected) or is taking drugs that increase sympathetic tone and could contribute to hypertension.

17. Individual has frequent intermittent or chronic pain that results in the 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 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: Female participants of childbearing potential 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 upper 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.

E STUDY PREPARATION PROCEDURES

E.1 Investigator/Investigational site selection

E.1.1 Investigator selection criteria

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 investigator may be included in the clinical study if compliant with the following requirements: appropriately qualified practitioners legally entitled to practice, and experienced in the diagnosis and treatment of patients requiring renal denervation.

E.1.2 Investigational site selection criteria

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

- Investigator should have adequate staff that is accessible and has time to manage the study.
- Investigator should have adequate staff to perform blinded blood pressure measurements.
- Investigator, and co-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 Clinical Investigation Plan and data collection requirements, including timely reporting of Adverse Events and Device Deficiencies as required by the Clinical Investigation Plan.
- 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 patients for three 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

E.1.3 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 Clinical Investigation Plan and subsequent amendments, by a fully executed agreement. Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

E.1.4 Curriculum Vitae

A current signed and dated Curriculum Vitae from the principal investigator, all co-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 3 years prior to the date of activation of the investigational site.

E.2 Ethics

E.2.1 EC/IRB approval

Here and throughout the document, “EC/IRB” is the term that will be used collectively in reference to an Institutional Review Board (IRB), Ethics Committee (EC), Medical Ethics Committee (MEC), Head of Medical Institution (HOMI), 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 Clinical Investigation Plan, 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 enrolment. 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 Clinical Investigational Plan (CIP), Investigator's Brochure (IB) (if applicable), Instructions for Use (IFU), Case Report Forms (CRF), Patient Information and Informed Consent Form and other study documents during study when revision(s) is determined necessary. Medtronic will submit revisions to the regulatory authorities and will also request that sites submit to their EC/IRB for review per national and local requirements.

In Japan, all protocol amendments will be reviewed by the sponsor and principal investigator. Upon agreement of the protocol changes, the Amended Protocol Signature Document must be signed or sealed and dated by the sponsor and investigator and submitted to the director of the investigational site according to the procedures of the investigational site. As necessary, the sponsor and investigator must comply with added requirements of IRB.

E.2.2 Patient Information and Informed consent process

The investigator or authorized designee must obtain written informed consent before any clinical study related activity takes place.

The patient will receive the EC/IRB-approved Patient Information (if required by geography) and Informed Consent Form. During the consent discussion the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Patient Information and the Informed Consent Form must be read aloud and explained. The language used shall be as non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

The patient must have ample time and opportunity to read and understand the Patient Information and the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the patient.

Neither the investigator, nor the investigational site staff shall coerce or unduly improper influence or induce a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the patient's rights.

When the patient decides to participate in the clinical study, the Patient Information and Informed Consent Form must be signed and personally dated by the patient and investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and Informed Consent Form was accurately explained and clearly understood by the patient, and that informed consent was freely given.

After all persons have signed and dated the Patient Information and Informed Consent Form, the investigator must provide the patient with a copy of the signed and dated Patient Information and Informed Consent Form.

A patient contact card will be made available to the patient with emergency contact numbers.

In Japan, the patient and investigator may provide their seal (with printed name) in lieu of a signature.

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

E.2.3 Revisions in Patient Information and Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject’s confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject’s confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC/IRB and local regulatory authority, if applicable. After approval by the EC/IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

E.2.4 Regulatory submission

In countries where submission to the regulatory authority is required per local law, no patients will be enrolled in the clinical study until the particular regulatory authority has approved the current Clinical Investigation Plan 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.

Other documents that are referred to in this Clinical Investigation Plan are listed below and will be made available upon request:

- Investigator’s Brochure (if applicable)
- Case Report Forms

E.3 Regulatory compliance

This clinical study will be conducted in compliance with Declaration of Helsinki 2013, the latest version of international standard ISO 14155 ('Clinical Investigation of medical devices for human subjects – Good Clinical Practice'), laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan. The study is compliant with the latest version of ISO14155 with the exception of adverse event collection after 12 months follow-up.

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).

21 CFR Part 54 (Financial Disclosure by Clinical Investigators), and Part 11 (Electronic Records; Electronic Signatures) apply to all geographies.

All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, EC/IRB approval, study training, preclinical testing, risk benefit assessment, publication policy, etc. This clinical study will also be registered on clinicaltrials.gov and study results posted based on the posting rules stipulated.

The sponsor will avoid improper influence on, or inducement of the subject, monitor, and investigator(s) or other parties participating in, or contributing to, the clinical study by implementing the informed consent process, Clinical Investigation Agreements, EC/IRB approval.

In Japan, the planning and conduct of this clinical study are subject to Japanese laws. It will begin only when all the requirements of the appropriate regulatory authority have been fulfilled. The study will also be conducted in accordance with the ethical principles of the Japan GCP Ordinance and the Pharmaceutical and Medical Device Act.

In Canada,the study will be conducted under an Investigational Testing Authorization in compliance with Medical Devices Regulations, SOR/98-282, Section 79-88.

E.4 Training requirements

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 clinical investigation plan, 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
- Case report form (CRF) completion and management, including electronic data entry
- Investigator and sponsor responsibilities
- Procedures for obtaining informed consent
- Investigational Review Board (IRB)/ Ethics Committee (EC) 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

E.5 Clinical study materials and clinical study-specific equipment

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

Medtronic will control the supply of devices and study materials. Investigational devices will not be sent to the site until receipt of or completion of the following:

- Curriculum vitae of the principal investigator, (if applicable) co-investigators and all key site staff.
- A signed Clinical Trial Agreement
- Financial disclosure from the investigators
- Competent Authority/FDA approval (as applicable to the geography)
- A copy of the IRB/EC approval letter, along with the voting roster
- The IRB/EC approved Patient Information and Informed Consent Form
- Documented training of the Principal Investigator, at a minimum
- Delegated Task List
- Lab certificate and lab normal values/ranges
- Confirmation of adequacy of equipment/facilities (e.g. a quiet room to perform the blood pressure measurements)

E.6 Study device/product handling and traceability

The Symplicity Spyral™ catheter and Symplicity G3™ generator must be stored as labeled at all sites. In countries where the product is investigational (Canada, the US, and Japan) and in countries where product is provided by Medtronic for purposes of the study and commercially available, product must be placed in a secure/locked location that meets the labeling requirements for device storage. 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)
- 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 the study enrollment and crossover period, and all remaining investigational devices must be returned to Medtronic.

The Symplicity Spyral™ catheter and Symplicity G3™ RF generator are commercially available in Europe and Australia and will be used within approved labelling for this study.

E.6.1 Supply of investigational devices/products

E.6.2 Storage and handling of investigational devices/products

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. In addition, all information for the use, storage and handling of the investigational device/product as indicated in the Instructions for Use and User Manual must be taken into account.

E.6.3 Device return procedures/products

Non-functioning investigational devices must be returned to Medtronic as soon as possible for investigation.

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
Attn: Service and Repair

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

Symplicity G3™ generator (Japan only)
Plexus Manufacturing Sdn Bhd (Hillside)
Bayan Lepas Free Industrial Zone
Phase II, 11900 Bayan Lepas
Pulau Pinang, Malaysia

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

E.6.4 Device/product disposition requirements

Investigational devices/products will be traced during the clinical study by assigning specific serial numbers to each device/product. The investigator is responsible for maintenance of a Device Tracking Log in the Investigator Site File. On this log, the receipt, use, return and disposal of the investigational devices/products shall be documented. At the end of the clinical study the principal investigator must sign and date the original Device Tracking Log.

F STUDY METHODS

F.1 Point of enrollment

Patients will be pre-screened for potential enrollment in the clinical study based on prior medical history and records of office SBP. A pre-screening log will be maintained to determine the number of patients that do not meet study eligibility criteria and who will not be approached for participation in the study.

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 consent must have been obtained prior to Screening Visit 1 (SV1).

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

A schedule outlining protocol required visits and assessments for subjects enrolled in the study is displayed in Table 4. A flowchart depicting the study design overview is provided in

Figure **12**. The following procedures will be followed for all subjects, excluding crossovers, enrolled in this study until study exit.

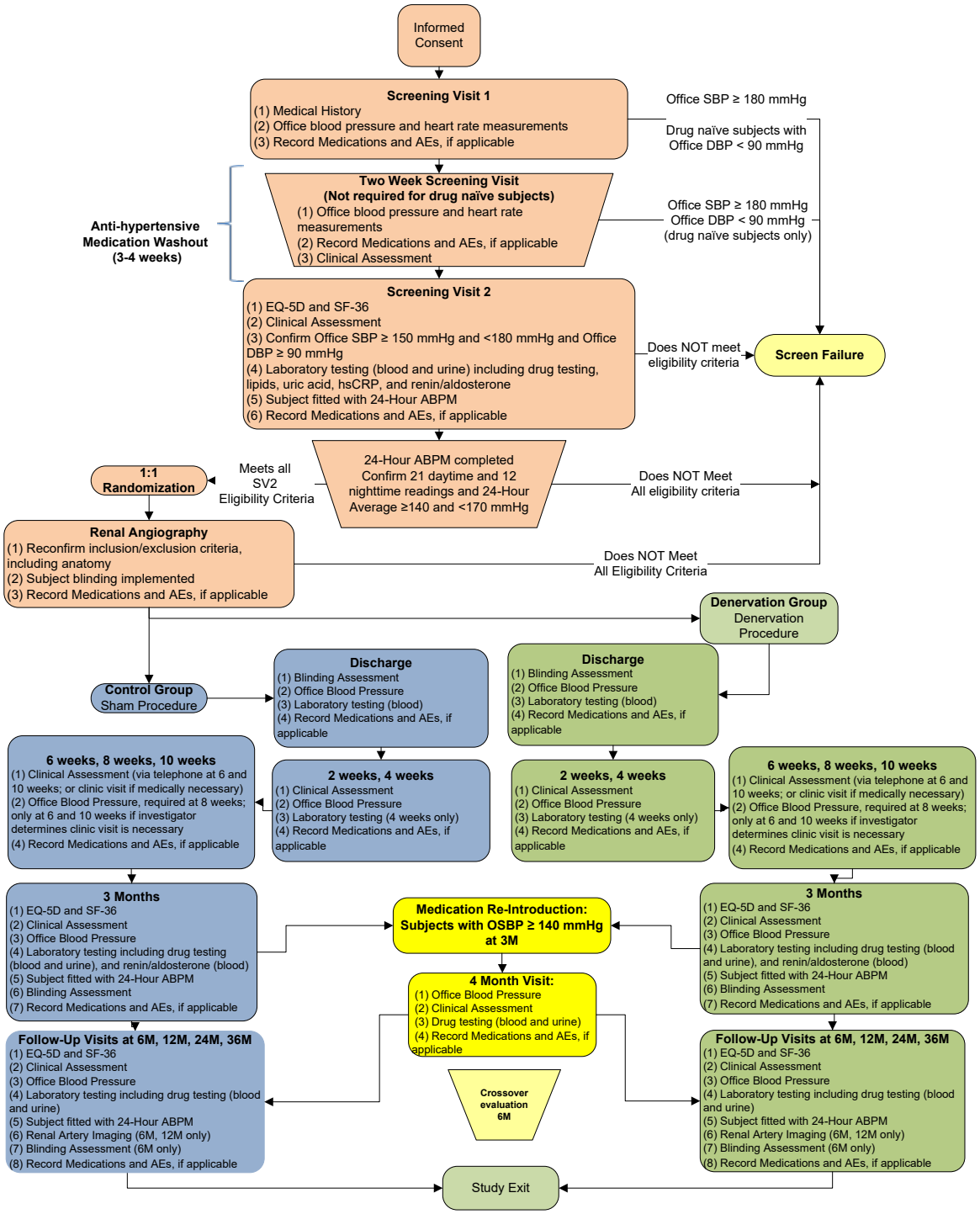

Figure 12: Study Design Overview

F.2 Screening Visit 1

After confirmation that the investigator or authorized designee and subject have personally signed and dated Patient Information and Informed Consent Form, the following assessments will be performed at Screening Visit 1:

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 Appendix L.7. 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.

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

Notification to the subject's family physician (i.e., the primary physician caring for the patient) of the subject's participation in the study will be made by mail 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 from the time of randomization until after the 6 month follow-up visit as this would impact the major endpoint of the study.

F.3 Medication Washout Period

Subjects not on antihypertensive medication(s) for a minimum of 4 weeks prior to SV1 are considered drug naïve and can proceed directly to SV2, within 3-4 weeks.

Following completion of Screening Visit 1, subjects on antihypertensive medication must be titrated off all antihypertensive medications over a 3-week washout period in a manner specified by the investigator. The washout period may be extended 1 additional week per investigator's discretion if it is judged necessary to allow the subject's blood pressure to stabilize off medications. Subjects with an office systolic blood pressure of <180 mmHg after the minimum 3-week washout period 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 period until procedure will be considered Screen Failures and will be exited from the study, as described in the *Subject Exit from Study* section of this Clinical Investigation Plan.

F.4 Two 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 patients do not need this visit. The target date is 2 weeks from the Screening 1 visit ± 3 days.

a. **Office Blood Pressure** measurements will be obtained in accordance with Appendix L.7. 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.

b. **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.

c. **Medication & Adverse Event Reviews** will be completed to document baseline medication use and adverse events that occur after enrollment.

F.5 Screening Visit 2

Screening Visit 2 must occur within 3-4 weeks of completion of SV1. The following assessments will be performed at Screening Visit 2:

a. **EQ-5D:** The EuroQol (EQ-5D) instrument will be administered to measure baseline health outcomes.

b. **SF-36**: The 36-Item Short Form Survey (SF-36) instrument will be administered to measure baseline health outcomes.

c. **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.

d. **Office Blood Pressure** measurements will be obtained in accordance with Appendix L.7. 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.

e. **Laboratory Tests:**

- **Basic metabolic panel Chem-7 (blood):** serum-creatinine, sodium, potassium, blood urea nitrogen (BUN), bicarbonate, chloride and glucose. Bicarbonate will not be measured for subjects enrolled in Japan and Europe.

- **Lipid Panel and hs-CRP (blood)**: total cholesterol, HDL, LDL, and triglycerides, as well as high sensitive-C reactive protein test are intended to evaluate a subject's cardiovascular risk profile. High-sensitivity CRP is not required to be measured for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed.

- **Uric Acid (blood):** This test is intended to potentially identify a marker for the renal denervation therapy responders.

- **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 or the local Japanese criteria for subjects enrolled in Japan The equation for estimated Glomerular Filtration Rate (eGFR) calculation method for Japanese is as follows:

  eGFR (mL/min/1.73 m^2) = 194 x $(sCr)^{-1.094}$× $(Age)^{-0.287}$ x (0.739 if female)

  Japanese Society of Hypertension Guidelines (JSH 2014), Hypertension Research (2014) 37, 266–278.

  Note: If eGFR ≥42 and <45 mL/min/1.73m² then patient 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 post-menopausal

- **Renin and Aldosterone (blood):** Samples should be collected in the morning after the patient has been out of bed for ≥2 hours and after resting quietly sitting for a minimum of 5 minutes but preferably 30 minutes. The time of day and subject's position (standing, sitting, or lying down) when the blood sample is collected should be documented and the same time of day (± 2 hours) and subject position should be used for collection of blood samples for determination of renin and aldosterone at later time points in the study.

- **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.

f. **24-hour Ambulatory Blood Pressure Monitoring** 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 randomization (procedure or control) 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 L.7. If ABPM is repeated office blood pressure and drug testing must be repeated on day the ABPM is applied.

g. **Adverse Event Reviews** will be completed to document adverse events that occur after enrollment.

h. **Baseline Renal Imaging** Submit a baseline Duplex Ultrasound, CT, or MRA if obtained per standard of care prior to procedure within one year from the date of the screening visit 1 and upload via Intelemage or send via courier.

Subjects determined to not be eligible for randomization will be exited from the study, as described in the Subject Exit from Study section of this Clinical Investigation Plan.

It is expected that subjects who are eligible to continue to randomization 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 2 weeks following Screening Visit 2. Randomization confirmation and the control or denervation procedure will occur once all eligibility criteria have been met as evaluated at Screening Visit 2 and the renal angiogram.

F.6 Procedure

Renal Angiography and Randomization Visit

Reconfirm Key Inclusion/Exclusion Criteria: To re-confirm that subjects still meet previously assessed eligibility criteria.

Renal Angiography and Blinding
All medication used should be commercially available in the respective geographies and compliant with local labeling. 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 (e.g., heparin or heparin analog in case of a documented heprin allergy should be initiated to maintain an ACT ≥ 250 sec during the procedure for control and treatment groups). While these subjects are not to be taking antihypertensive medications following SV1 until 3 months following randomization, either 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 subjects blinded to treatment allocation according to methods outlined in section C.5 to confirm eligible renal artery anatomy. Ensure subject received a minimum aspirin dose of 250 mg intravenous (per local drug dose labelling) or up to 325 mg oral (per local drug dose labelling) prior to procedure unless patient was already taking aspirin on a regular basis. If the patient 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 (per local drug dose labelling); under these circumstances, a loading dose of at least 150 mg clopidogrel may be administered prior to the procedure per physician discretion.

In Japan, Canada, and Australia, use of antiplatelet agents should follow the hospital's protocol for renal angiography.

Control Group

Subjects will be blinded during the renal angiogram by a combination of conscious sedation, sensory isolation (e.g., blindfold and music), and lack of familiarity the procedural details and duration (i.e., subjects will not know the difference between the renal angiography procedure alone and the renal angiography and denervation procedure). If randomized to the Control Group, subjects will remain blinded and remain on the catheterization lab table for at least 20 minutes prior to introducer sheath removal. Details of blinding procedure are described in C.5.

Denervation Procedure

If randomized to treatment, the renal artery denervation procedure will be performed according to the supplied Symplicity Spyral™ catheter Instructions for Use, Symplicity G3™ generator User Manual and associated training provided by Medtronic.

Consider pre-treatment with both anxiolytic medications and analgesic medications, such as morphine sulfate or fentanyl (with additional doses timed with ablation treatments as appropriate). 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. Investigators should make an attempt to apply treatment to any renal artery that meets the anatomy eligibility criteria. The Symplicity Spyral™ catheter will be inserted into the renal artery and the ablation treatments at multiple positions along the renal artery will be performed.

Medtronic recommends performing ablations in all accessible renal arterial vessels between 3 and 8 mm in diameter including accessory, branch and main renal arteries that are outside the kidney parenchyma.

Note: Initial placement of the Symplicity Spyral™ catheter should be just proximal to the renal parenchyma as identified on fluoroscopic imaging. Perform as many ablations within a segment as anatomy permits starting distally and working proximally without overlapping treatment zones. Avoid ablations in a bifurcation and within 5mm of areas with calcification atheroma or stented lesions. If the vessel segment cannot accommodate all 4 electrodes, then it is suggested to either 1) position a smaller number of electrodes and deselect electrodes, or 2) advance all electrodes within the renal artery vessel segment and deselect the distal electrodes.

Upon completion of denervation procedure for the Denervation group subjects, or renal angiogram for Control subjects, 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 antihypertensive medications for BP 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.

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 Medtronic, loaded into the Case Report Form and submitted to Medtronic Research and Development Department.

Post-procedure care

All randomized subjects will be hospitalized overnight following the renal angiogram and standard-of-care post-intervention monitoring procedures will be followed, while ensuring blinding is maintained.

Prior to discharge, the subject and BP assessor will complete a blinding assessment form and 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 blinded study personnel. In case of a crossover, anti-HTN meds, if applicable, will not be required to be withheld prior to this office blood pressure assessment. 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 him/her at the required follow-up times (e.g., home, work, cell, and primary physician).

Patients shall be prescribed a minimum of 75 mg aspirin for 1 month post-procedure. All medication used should be commercially available in the respective geographies and compliant with local labeling. If the subject has a documented allergy to aspirin, at least 75 mg clopidogrel per day for 1 month post-procedure may be prescribed. Use of antiplatelet agents in Japan, Canada, and Australia should follow the hospital's protocol for renal angiography.

F.7 Follow-Up Procedures

Subjects will return for in-office follow-up visits at week 2, 4 and 8 (±3 days) post-procedure. A phone call follow-up will be conducted at week 6 and 10 (±3 days) post-procedure. There will additionally be follow-up visits at 3 and 6 months (±14 days) post-procedure. Upon completion of the 3 month follow-up visit, a Medication Re-Introduction protocol to resume antihypertensive medications must be followed, if required. See instructions in Section F.9 for Medication Re-Introduction for Subjects with Systolic OBP ≥ 140 mmHg at 3M follow-up visit. Subjects will then return at 6 months (± 14 days) ,12, 24, and 36 months post-procedure with visits conducted ± 30 days, from the procedure date. In case of a crossover, subjects will return for in-office visits at 1, 3, 6, 12 and 24 months post-crossover procedure.

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, i.e. home health care personnel. The following assessments maynot 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.

In the event an in-home visit is not possible, the alternate methods for obtaining follow-up assessments are listed below:

- Virtual Visit, i.e. inclusive of video with study subject. The following assessments may not be completed with a virtual 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 the study site.
    - Renal Artery Imaging:
        - Make every effort to scheduled in-person renal artery imaging as soon as possible.
        - When possible, subjects may 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 measurements may be collected and designated as subject-reported in the case report form.
        - Office blood pressure and ABPM units to be provided to the subjects in advance of the visit by the study site.
    - Witnessed pill intake prior to ABPM.
        - Documentation of pill intake will be assessed virtually.
- Phone Visit, i.e. no video with the subject. The following assessments may not be completed with 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. 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 measurements may be collected and designated as subject-reported in the case report form.
        - Office blood pressure and ABPM units to be provided to the subjects in advance of the visit by study site.
    - Witnessed pill intake prior to ABPM.

- Documentation of pill intake will be assessed over the phone as confirmed verbally by subject.

In case the Symplicity Spyral™ catheter and Symplicity G3™ generator receive commercial approval in the United States, Canada and/or Japan during the course of this clinical study, the follow-up assessments will continue to be conducted as planned unless otherwise instructed.

Follow-up procedures for all subjects are listed below. Follow-up procedures must be performed by blinded site personnel through 6 months follow-up for each subject.

a) **EQ-5D:** The Euro-Qol 5D (EQ-5D) will be administered at the 3, 6, 12, 24 and 36 month post-procedure visits to measure health outcomes.

b) **SF-36:** The 36-Item Short Form Survey (SF-36) will be administered at the 3, 6,12, 24 and 36 month post-procedure visits to measure health outcomes.

c) **Clinical Assessment** will be conducted at all post-procedure follow-up visits to evaluate the subject's current 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.

d) **Office Blood Pressure** measurements will be obtained in accordance with Appendix L.7 at all post-procedure follow-up visits.

e) **Laboratory Tests:**

- **Basic metabolic panel Chem-7 (blood):** serum-creatinine, sodium, potassium, blood urea nitrogen (BUN), bicarbonate, chloride and glucose. Bicarbonate will not be measured for subjects enrolled in Japan and 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 or the local Japanese criteria for subjects enrolled in Japan.

- **Renin and Aldosterone testing (blood; 3 month follow-up only)** Samples should be collected in the morning after the patient has been out of bed for ≥2 hours and after resting quietly after a minimum of 5 minutes but preferably 30 minutes. The time of day and subject's position (standing, sitting, or lying down) before the blood sample is collected should be documented and the same time of day (± 2 hours) and subject position should be used for collection of blood samples for determination of renin and aldosterone at later time points in the study.

- **Drug testing (urine/blood)** to ensure no medications are present in the subject's system at 3 months follow-up and to ensure that prescribed medications are in the subject's system at 6, 12, 24, and 36 months. 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.

f) **Initiate Medication Re-Introduction for Subjects with Systolic OBP ≥ 140 mmHg at 3M follow-up visit.** Starting at 3 month follow-up after clinical assessment and a valid ABPM are completed.

g) **Medication & Adverse Event Reviews** will be completed at each follow-up visit to assess any changes in medication usage or medical condition**:**

- **Enrollment (consent) to 12-months post procedure:** all medications and all adverse events
- **12 to 36 months post-procedure:** all medications and serious adverse events only. Previously reported adverse events will be followed up through resolution until the end of the study.

h) **Renal Artery Imaging** will be performed at the 6-month post-procedure visit to assess if a renal artery stenosis is suspected. A renal duplex ultrasound (DUS) will be obtained at 6M 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 recommended 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 Laboratories, an angiogram must be obtained and submitted to the Angiographic Core Laboratory.

- A renal duplex ultrasound (DUS) at 6-month follow-up is not required for subjects randomized to the control group who are crossing over, if they are having the renal denervation procedure done within 30 days of their 6 month follow-up visit. If they are not having the renal denervation procedure done within the 30 days of their 6 month follow-up visit, a renal duplex ultrasound (DUS) is required.
- The 12-month renal imaging will be required for all randomized subjects. If the renal imaging is determined to be nondiagnostic, a repeat DUS, MRA, CTA or angiogram will be performed. If repeat DUS, CTA, or MRA is nondiagnostic or evidence of a clinically significant stenosis (>60-70%) is indicated, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month visit follow up at the time of protocol approval will be required to undergo renal imaging at their next scheduled follow-up visit unless they have a renal angiogram due to crossover.For participating sites in Germany and the UK, only DUS or renal MRA imaging at the 12-month follow-up visit (or 24M or 36M follow-up as applicable) will be performed. For these countries, if the initial DUS or initial renal MRA is non-diagnostic, a repeat DUS or repeat renal MRA should be performed. If the initial imaging modality or subsequent repeat(s) are non-diagnostic, the investigator should choose the repeat imaging modality (DUS or MRA) that is expected to yield the required information for a diagnostic study.

i) **24-hour Ambulatory Blood Pressure Monitoring** will be conducted at each visit from the 3 month to the 36 month follow-up visits post-procedure according to the guidelines in Appendix L.7. 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 must be repeated on day the ABPM is applied ().

j) **Blinding Assessment** will be requested from all study subjects and study staff assessing BP at the 3- and 6-month follow-up visits to assess validity of the study blinding.

k) **Mortality Assessment** will be completed by the investigational site when a subject cannot be reached after each of the protocol required follow-up visits..

F.8 Escape Medication Protocol during Off Medication Period

In the event a subject's office SBP ≥180 mmHg or there is a safety concern, from randomization 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 2 weeks 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 6. If the subject's office SBP< 180 mmHg, the subject will continue to be followed per Table 4. 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 8. All blood pressures must be taken according to the guidelines in Appendix L.7 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 eCRF. Escape subjects randomized to the Control (sham) group may be offered renal denervation therapy (crossover) after their 6- month follow-up visit. Refer to Section F.10 for crossover procedures.

F.9 Medication Re-Introduction for Subjects with 3M Systolic OBP ≥ 140 mmHg

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 L.7.

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

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 antihypertensive medication regimen are made between 3 and up to 6 months post-procedure, complete an unscheduled follow-up visit, and obtain an Office Blood Pressure according to the guidelines in Appendix L.7. In addition, all medication changes are to be documented on the eCRF. All medication used should be commercially available in the respective geographies and compliant with local labeling.

F.10 Crossover Procedures

Control subjects may crossover and receive renal denervation therapy at or after their 6 month follow-up visit. For the subjects who had already completed their 6 month visit, the decision to crossover must take place at their next in person visit. All subjects will have 30 days from the Crossover visit (6, 12, 24 , 36 month follow-up or Unscheduled visit) to undergo the crossover procedure. Subjects who are more than 30 days from their 6, 12, 24 or 36 month, must complete a crossover Baseline visit prior to crossing over. Control subjects who are coming in for their scheduled 6, 12, 24 and 36 month follow-up visit do not need to come in for a crossover Baseline visit if all the required crossover Baseline procedures occurred, including lipid panel, hs-crp and uric acid blood tests. To crossover, the subject cannot meet any of the anatomical and glomerular filtration rate (eGFR) exclusion criteria, and cannot be pregnant, nursing or planning to become pregnant during the course of the study follow-up.Crossover subjects will undergo follow-up visits at 4 weeks, 3, and 6 months (± 14 days) post-procedure and annually at 12 and 24 months (± 30 days) post-procedure. Follow-up procedures post-crossover procedure are listed below. Subjects who do not meet required eligibility criteria for crossover on the day of the procedure will undergo follow-up visits according to their original follow-up schedule. Crossover will not be offered at a later time if it was declined by control subjects during the allowed 30-day window.

Baseline Crossover Data:

Control subjects who are coming in for their scheduled 6, 12, 24, 36-month or Unscheduled follow-up visits do not need to come in for a crossover baseline visit if all required crossover baseline procedures occurred during the respective follow-up visit, as listed below. An in-office visit is required for the baseline crossover visit assessments. Note, if the lipid panel, hs-CRP and uric acid were collected at SV2, these tests will not be required to be repeated. If the lipid panel, hs-CRP and uric acid was not collected at SV2, they will need to be collected within 30 days prior to the crossover procedure. For subjects accepting crossover at their 6-month visit, the 6-month DUS is not needed, if the subject has the crossover procedure within 30 days of the visit.

a) **Clinical Assessment** will be conducted.

b) **Office Blood Pressure** measurements will be obtained in accordance with Appendix L.7.

c) **Laboratory Tests:**

- **Basic metabolic panel Chem-7** (blood)): serum-creatinine, sodium, potassium, blood urea nitrogen (BUN), bicarbonate, chloride and glucose. Bicarbonate will not be measured for subjects enrolled in Japan and Europe.

- **Lipid Panel and hs-CRP (blood) (prior to procedure, If not already collected at SV2)**: total cholesterol, HDL, LDL, and triglycerides, as well as high sensitive-C reactive protein test are intended to evaluate a subject's cardiovascular risk profile. High-sensitivity CRP is not required to be measured for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed.

- **Uric Acid (blood) (prior to procedure, If not already collected at SV2):** This test is intended to potentially identify a marker for the renal denervation therapy responders.

- **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 or the local Japanese criteria for subjects enrolled in Japan.

- **hCG (prior to procedure)** pregnancy test in blood/urine for female subjects who are not post-menopausal.

- **Drug testing (urine/blood)** to ensure prescribed medications are 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.

d) **Medication & Adverse Event Reviews** will be completed to assess any changes in medication usage or medical condition,

e) **Witnessed pill taking prior to ABPM** will be undertaken, if applicable. Subjects will be instructed to not take their antihypertensive medications on the day of the office visit and to bring their medications with them. Visits will start prior to 10:30am for all patients who take their antihypertensive medications in the morning. Afternoon visits will be allowed for subjects that take their antihypertensive medications in the afternoon. Study personnel should document pill identity and observe the subject swallowing the antihypertensive medication(s). Once this is completed and documented, the ABPM device should be applied to the subject and the recording started before leaving the office.

f) **24-hour Ambulatory Blood Pressure Monitoring** will be conducted at the 3, 6, 12, and 24-month post-procedure follow-up visits to evaluate the subject's

ambulatory blood pressure according to the guidelines in Appendix L.7. 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 must be repeated on day the ABPM is applied.

Crossover Follow-Up Data:

Crossover subjects will undergo follow-up visits at 1, 3, and 6-months (± 14 days) post-procedure and annually at 12 and 24-months (± 30 days) post-procedure. Follow-up procedures post-crossover procedure are listed below. Subjects who do not meet required eligibility criteria for crossover on the day of the procedure will undergo follow-up visits according to their original follow-up schedule.

a) **EQ-5D:** The Euro-Qol 5D (EQ-5D) will be requested at the 3, 6, 12 and 24 month post-procedure visits to measure health outcomes.

b) **SF-36**: The 36-Item Short Form Survey (SF-36) will be administered at the 3, 6,12 and 24 month post-procedure visits to measure health outcomes.

c) **Clinical Assessment** will be conducted at all post-procedure follow-up visits to evaluate the subject's current medical condition.

d) **Office Blood Pressure** measurements will be obtained in accordance with Appendix L.7 at all post-procedure follow-up visits.

e) **Laboratory Tests:**

- **Basic metabolic panel Chem-7** (blood)): serum-creatinine, sodium, potassium, blood urea nitrogen (BUN), bicarbonate, chloride and glucose. Bicarbonate will not be measured for subjects enrolled in Japan and 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 or the local Japanese criteria for subjects enrolled in Japan.

f) **Medication & Adverse Event Reviews** will be completed at each follow-up visit to assess any changes in medication usage or medical condition**:**

- **Procedure to 12-months post-procedure:** all medications and all adverse events

- **After the 12-month visit through 24 months post-procedure:** all medications and serious adverse events only. Previously reported adverse events will be followed up through resolution until the end of the study.

g) **Renal Artery Imaging** will be performed at the 6-month post-crossover procedure visit to assess if a renal artery stenosis is suspected. A renal duplex ultrasound (DUS) will be obtained and submitted to the DUS Core Laboratory. If the DUS is determined to be nondiagnostic (not evaluable), a repeat DUS, a MRA, CT or angiogram will be performed. If evidence of a clinically significant stenosis is indicated by the DUS or MRA/CT Core Laboratories, an angiogram must be obtained and submitted to the Angiographic Core Laboratory.

- The 12-month post-crossover renal DUS, CTA or MRA will be required. If the DUS, CTA or MRA is determined to be nondiagnostic, a repeat DUS, CTA, MRA or angiogram will be performed. If repeat DUS/CTA/MRA is nondiagnostic or evidence of a clinically significant stenosis (>60-70%) is indicated, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month visit follow up at the time of protocol approval will be required to undergo renal imaging at their next scheduled follow-up unless they have a renal angiogram due to crossover.

    i. For the participating sites in Germany and the UK, only renal MRA imaging at the 12-month follow-up visit (or 24 or 36M follow-up as applicable) will be performed. For these countries, if the initial MRA is non-diagnostic, a repeat MRA should be performed. If the initial MRA or repeat renal MRAs are non-diagnostic and an additional repeat MRA is not expected to yield the required information for a diagnostic study, a DUS can be completed.

h) **24-hour Ambulatory Blood Pressure Monitoring** will be conducted at the 3, 6, 12, and 24-month post-procedure follow-up visits to evaluate the subject's ambulatory blood pressure according to the guidelines in Appendix L.7. 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 must be repeated on day the ABPM is applied.

i) **Mortality Assessment** will be completed by the investigational site when a subject cannot be reached after each of the protocol required follow-up visits.

F.11 Confirmatory Blood Draws 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.

F.12 Drug testing for Emergency Room visit or Hospitalization for Elevated Blood Pressure

In the event a study subject is hospitalized or presents to the emergency room for elevated BP, the subject should be instructed to have site personnel notified and site personnel should attempt to obtain a urine and blood sample for antihypertensive drug testing to confirm if subject was complying with medication requirements as per the protocol. This can be obtained up to 24 hours after the subject has been discharged

F.13 Data collection requirements

All study data will be entered into electronic Case Report Forms (eCRFs) in a database provided by the Sponsor. All eCRFs will be completed using de-identified data.

eCRF completion may be delegated by the Principal Investigator (documented on the Delegated Task List) to other study personnel but the Principal Investigator remains responsible for the accuracy and integrity of all data entered in eCRFs.

Additional details regarding procedures used for data review, database cleaning, issuing and resolving data queries, and identification of steps for creation, modification, maintenance, archiving retrieval or transmission of source data via any computerized systems will be provided in the study specific Data Management Plan (DMP).

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 (ABPM)

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.

Medtronic will be responsible for annual maintenance of the Symplicity G3™ generator and calibration of the Office Blood Pressure and ABPMs according to the manufacturer's requirements. Documentation of the routine maintenance will be provided to the study site upon completion.

Table 4: Schedule of Testing for All Subjects (See 5 for Crossover Subjects' Testing)

3 Months (90 days): 76-104 days 24 Months (720 days): 690-750 days
4Months (120 days):113 -127 days
6 Months (180 days): 166-194 days 36 Months (1080 days): 1050-1110 days
12 Months (360 days): 330-390 days

							Post-Procedure (Wk= ± 3 days) (M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-36M visits)										
Required Assessments	**SV1**	**3 Wk Washout (minimum)with screening visit at Wk 2 (see next column)**	**2 Wk visit (Screening) ± 3 days**	**SV2 (within 3-4 Wk of SV2)**	**Procedure**	**Prior to Discharge**	**2Wk**	**4Wk**	**6Wk**	**8Wk**	**10Wk**	**3M**	**4m visit for BP≥ 140 mmHg at 3m (±7days)**	**6M**	**12M**	**24M**	**36M**
Medical History	X																
Clinical Assessment			X	X			X	X	X[3]	X	X[3]	X	X	X	X	X	X
Prescribe Medications according to section F.9)												X	X				
Witnessed pill intake (if subject is taking antihypertensive medications), Complete after OBP measurements.														X	X	X	X

3 Months (90 days): 76-104 days 24 Months (720 days): 690-750 days
4Months (120 days):113 -127 days
6 Months (180 days): 166-194 days 36 Months (1080 days): 1050-1110 days
12 Months (360 days): 330-390 days

							Post-Procedure **(Wk= ± 3 days) (M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-36M visits)**									
Required Assessments	**SV1**	**3 Wk Washout (minimum)with screening visit at Wk 2 (see next column)**	**2 Wk visit (Screening) ± 3 days**	**SV2 (within 3-4 Wk of SV2)**	**Procedure**	**Prior to Discharge**	**2Wk**	**4Wk**	**6Wk**	**8Wk**	**10Wk**	**3M**	**4m visit for BP≥ 140 mmHg at 3m (±7days)**	**6M**	**12M**	**24M**	**36M**
Renal Denervation or Sham Procedure					X												
Office Blood Pressure according to guidelines in Appendix L.7	X		X	X		X	X	X	X[3]	X	X[3]	X	X	X	X	X	X
24-Hour ABPM according to guidelines in Appendix L.7				X								X		X	X	X	X
Blood Tests (uric acid, lipid panel and high-sensitivity CRP[7] (hs-CRP))				X													

3 Months (90 days): 76-104 days 24 Months (720 days): 690-750 days
4Months (120 days):113 -127 days
6 Months (180 days): 166-194 days 36 Months (1080 days): 1050-1110 days
12 Months (360 days): 330-390 days

							Post-Procedure (Wk= ± 3 days) (M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-36M visits)										
Required Assessments	**SV1**	**3 Wk Washout (minimum)with screening visit at Wk 2 (see next column)**	**2 Wk visit (Screening) ± 3 days**	**SV2 (within 3-4 Wk of SV2)**	**Procedure**	**Prior to Discharge**	**2Wk**	**4Wk**	**6Wk**	**8Wk**	**10Wk**	**3M**	**4m visit for BP≥ 140 mmHg at 3m (±7days)**	**6M**	**12M**	**24M**	**36M**
Blood Tests (Chem-7)[4]				X		X		X				X		X	X	X	X
Blood Tests (renin and aldosterone)				X								X					
Serum or Urine Pregnancy Test				X													
Drug testing				X								X	X	X	X	X	X
Renal Artery Imaging - Angiogram					X												
Renal Artery Imaging				X[5]										X[1]	X[6]	(X)[6]	(X)[6]
Blinding Assessment						X						X		X			
EQ-5D and SF-36				X								X		X	X	X	X

3 Months (90 days): 76-104 days 24 Months (720 days): 690-750 days
4Months (120 days):113 -127 days
6 Months (180 days): 166-194 days 36 Months (1080 days): 1050-1110 days
12 Months (360 days): 330-390 days

							Post-Procedure **(Wk= ± 3 days) (M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-36M visits)**										
Required Assessments	**SV1**	**3 Wk Washout (minimum)with screening visit at Wk 2 (see next column)**	**2 Wk visit (Screening) ± 3 days**	**SV2 (within 3-4 Wk of SV2)**	**Procedure**	**Prior to Discharge**	**2Wk**	**4Wk**	**6Wk**	**8Wk**	**10Wk**	**3M**	**4m visit for BP≥ 140 mmHg at 3m (±7days)**	**6M**	**12M**	**24M**	**36M**
Mortality Assessment*[2]							X	X		X		X		X	X	X	X
Medication Review, Event Review	All adverse events (AE) and medication review. After 12 months, previously reported AEs will need to be reviewed and updated as needed															Serious AE and all medication review	

1 DUS is required as first line imaging modality. 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. The 6M DUS will not be required for subjects crossing over at 6M.

2 Conduct if follow-up missed.

3 If medically necessary, phone contact may be replaced with office visit. Office blood pressure (according to guidelines in Appendix L.7), only needs to be obtained if an office visit occurs.

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

5 Submit baseline duplex ultrasound, CT, or MRA if obtained per standard of care within one year from the date of Screening visit 1.

6 DUS/CTA/MRA required as first line imaging modality at 12M (and 24M and 36M as applicable). Repeat DUS, MRA, or CTA to be used if prior imaging modality is nondiagnostic. If repeat DUS/CTA/MRA is nondiagnostic or evidence of a clinically significant stenosis (>60-70%) is indicated, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month without renal imaging will be required to undergo renal imaging at their next scheduled follow-up unless they have a renal angiogram due to crossover. For participating sites in Germany and the UK, only DUS or renal MRA imaging at the 12-month follow-up visit (or 24 or 36M follow-up as applicable) will be performed. For these countries, if the initial DUS or initial renal MRA is non-diagnostic, a repeat DUS or repeat renal MRA should be performed. If the initial imaging modality or subsequent repeat(s) are non-diagnostic, the investigator should choose the repeat imaging modality (DUS or MRA) that is expected to yield the required information for a diagnostic study.

7 High-sensitivity CRP is not required to be measured for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed

Table 5: Schedule of Testing for Crossover Subjects

1 Month (30 days): 14-44 days 3 Months (90 days): 76-104 days 24 Months (720 days): 690-750 days 6 Months (180 days): 166-194 days 12 Months (360 days): 330-390 days	**Post-Procedure** **(M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-24M visits)**

Required Assessments	**Baseline**	**Renal Denervation**	**Prior to Discharge**	**1M**	**3M**	**6M**	**12M**	**24M**
Clinical Assessment	X			X	X	X	X	X
Blood tests (uric acid, lipid panel and high-sensitivity CRP (hs-CRP))******		X (prior to procedure)*****						
Blood Tests (Chem-7)***	X		X	X	X	X	X	X
Office Blood Pressure according to guidelines in Appendix L.7	X		X	X	X	X	X	X
Serum or Urine Pregnancy Test		X (prior to procedure)						
Witnessed pill intake (if subject is taking antihypertensive medications), Complete after OBP measurements.	X				X	X	X	X
24-Hour ABPM according to guidelines in Appendix L.7	X				X	X	X	X
EQ-5D and SF-36					X	X	X	X
Renal Denervation		X						
Renal Artery Imaging - Angiogram		X						
Drug Testing	X				X	X	X	X

1 Month (30 days): 14-44 days 3 Months (90 days): 76-104 days 24 Months (720 days): 690-750 days 6 Months (180 days): 166-194 days 12 Months (360 days): 330-390 days	**Post-Procedure** **(M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-24M visits)**

Required Assessments	**Baseline**	**Renal Denervation**	**Prior to Discharge**	**1M**	**3M**	**6M**	**12M**	**24M**
Renal Artery Imaging						X*	X****	(X)****
Mortality Assessment**				X	X	X	X	X
Medication Review, Event Review	All adverse events (AE) and medication review After 12 months, previously reported AEs will need to be reviewed and updated as needed							Serious AE and all medication review

*DUS is required as first line imaging modality. Repeat DUS, MRA, CT or angiogram to be used if DUS is non-diagnostic. Renal angiography must be used if repeat DUS/CTA/MRA is nondiagnostic or stenosis >60-70% is suspected.

**Conduct if follow-up visit missed

*** Bicarbonate will not be measured for subjects enrolled Japan and Europe.

**** DUS/CTA/MRA required as first line imaging modality at 12M (and 24M as applicable). Repeat DUS, MRA, or CTA to be used if prior imaging modality is nondiagnostic. If repeat DUS/CTA/MRA is nondiagnostic or evidence of a clinically significant stenosis (>60-70%) is indicated, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month without renal imaging will be required to undergo renal imaging at their next scheduled follow-up. For participating sites in Germany and the UK, only DUS or renal MRA imaging at the 12-month follow-up visit (or 24M follow-up as applicable) will be performed. For these countries, if the initial DUS or initial renal MRA is non-diagnostic, a repeat DUS or repeat renal MRA should be performed. If the initial imaging modality or subsequent repeat(s) are non-diagnostic, the investigator should choose the repeat imaging modality (DUS or MRA) that is expected to yield the required information for a diagnostic study.

*****If not already collected at SV2

****** High-sensitivity CRP is not required to be measured for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed

Table 6: Schedule of Testing through 36 Months for Subjects with office SBP ≥180 mmHg (confirmed via 2 measurements) or Escape via Investigator Discretion during Off-Medication Period Post-randomization

			Post-Procedure (Wk= ± 3 days, M=months ± 14 days for 3M and 6M visits; ± 30 days for 12M-36M visits)									
Required Assessments	**Procedure**	**Prior to Discharge**	**2Wk**	**4Wk**	**6Wk**	**8Wk**	**10Wk**	**3M**	**6M**	**12M**	**24M**	**36M**
Office Blood Pressure according to guidelines in Appendix L.7		X	X	X	X	X	X	X	X	X	X	X
Renal Artery Imaging									X[1]	X[3]	(X)[3]	(X)[3]
Mortality Assessment[2]			X	X	X	X	X	X	X	X	X	X
Medication Review, Event Review	All adverse events (AE) and medication review After 12 months, previously reported AEs will need to be reviewed and updated as needed										Serious AE and all medication review	

1 DUS required as first line imaging modality. 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.

2 Conduct if follow-up visit missed

3 DUS/CTA/MRA required as first line imaging modality at 12M (and 24M and 36M as applicable). Repeat DUS, MRA, or CTA to be used if prior imaging modality is nondiagnostic. If repeat DUS/CTA/MRA is nondiagnostic or evidence of a clinically significant stenosis (>60-70%) is indicated, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month without renal imaging will be required to undergo renal imaging at their next scheduled follow-up. For participating sites in Germany and the UK, only DUS or renal MRA imaging at the 12-month follow-up visit (or 24 or 36M follow-up as applicable) will be performed. For these countries, if the initial DUS or initial renal MRA is non-diagnostic, a repeat DUS or repeat renal MRA should be performed. If the initial imaging modality or subsequent repeat(s) are non-diagnostic, the investigator should choose the repeat imaging modality (DUS or MRA) that is expected to yield the required information for a diagnostic study.

F.14 Role of sponsor's representatives

Sponsor's representatives will provide support as required for the clinical study, including but not limited to technical support during the procedure and/or technical support during follow-up in order to ensure that all study requirements are met and the procedure is performed according to the Instructions for Use. The sponsor's representatives providing technical support may be listed on the sponsor technical support list.

F.15 Source documents

Data entered in the eCRF 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 patient eligibility criteria.

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

The eCRFs (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 eCRFs was derived. 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 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 source documents will be requested to support event adjudication by the Clinical Events Committee. In Japan, availability of source documentation may be limited due to hospital policies. If a specific source document is not available, necessary information may be transcribed onto the relevant CRF page.

F.16 Adverse events and device deficiencies

F.16.1 Definition/classification

For each reported adverse event, the Investigator will assess the events in terms of relationship to the device, relationship to the procedure, 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 7 days post-procedure *(or post-denervation in the case of a control group subject being denervated at cross over)* 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 the latest version of International Organization of Standardization (ISO) ISO 14155.

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.

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 use error or from intentional misuse of the investigational medical device

Note 3: This includes a "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.

Serious Adverse Event (SAE): ***(ISO 14155 3.37)***
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 including chronic diseases, or
c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment.

NOTE: 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 3.36)***

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event

Unanticipated Serious Adverse Device Effect (USADE): ***(ISO 14155 3.42)***
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

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) CRF 21 Part 11 the following definitions will apply:

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

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.

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

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.

F.16.2 Recording, reporting, and review of Adverse Events

Adverse Event (AE) information will be collected by the site from subject enrollment (consent) through study termination or study exit per table 8 reporting requirements. AEs will be followed until the event has resolved or study completion, which ever comes later (in the case of permanent impairment, the event will be followed until it stabilizes and the overall clinical outcome has been ascertained).

The Investigator will report any adverse events that may occur to the Sponsor, and will indicate the date of the 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 or not 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.

A list of AEs that may be associated with the use of the investigational device and/or the interventional procedure is provided in the Risks section (Section J.2).

Events that do not qualify as AEs:

- 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 AEs (see Table 7)

Table 7: 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

Event Description	Time Frame (hours) from the Renal Denervation Procedure
Elevated blood pressure	During the procedure

In Japan, all adverse event information (including Unavoidable AEs) will be collected by the site.

Onset of any events listed in Table 7 after the specified timeframes and/or events lasting longer than the specified timeframe (if onset is at the time of procedure) should be reported as an AE.

All Adverse Events, regardless of relatedness or outcome, must be reported up until 12 months. After 12 months, only SAEs are to be reported. Adverse events will be documented on the appropriate case report form, 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 eCRF, one eCRF for each Adverse Event term. See the Adverse Event eCRF for the information to be reported for each Adverse Event and Table 8 for the event reporting timeframe requirements. For Adverse Events that require immediate reporting (Table 8), initial reporting will be done on the eCRF by completing as much information as is available. The AE eCRF must be "saved as Complete" in the Remote Data Capture (RDC) system to ensure it is reported to Medtronic as soon as possible.

All Adverse Events and Device Deficiencies will be reviewed by the Medtronic Safety Department. This review will include the determination whether the Adverse Event meets regulatory reporting requirements (seeTable 8). The Sponsor will ensure timely Adverse Event/ 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 promptly report this device related Adverse Event/Device Deficiency to the Medtronic Product Experience Management (PXM) Galway, Ireland. The Medtronic Product Experience Management (PXM) Galway, Ireland will ensure prompt review, and appropriate reporting.

UADE Evaluation and Reporting:

Medtronic will conduct an evaluation of the UADE in accordance with CFR 812.46(b) and shall report the results of such evaluation to 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.

F.16.3 Recording, reporting, and review of Device Deficiencies

Device deficiencies are defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance *(ISO 14155 3.19)*. Device deficiencies

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

Malfunction is defined as 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 [Ref. 21 CFR 803.3(m)]. Product labels, Instructions for Use, and User Manuals for this study are provided separately.

All device deficiencies and malfunctions will be documented on the appropriate case report form, reported to Medtronic, and reported to the ethics committee (if required) within the ethics committee 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 the Device Deficiency eCRF for the information to be reported for each Device Deficiency that did not lead to an Adverse Event.

Device deficiencies that did not lead to an Adverse Event but could have led to an SADE ***(ISO 14155 6.4.2)***

a) if either suitable action had not been taken,

b) if intervention had not been made, or

c) if circumstances had been less fortunate,

require immediate reporting (see Table 8). Initial reporting may be done by will be done on the eCRF by completing as much information as is available. The Device Deficiency (e)CRF must be “saved as Complete” in the Remote Data Capture (RDC) system to ensure it is reported to Medtronic as soon as possible.

F.16.4 Adverse Event Reporting Requirements

Investigator and Sponsor reporting requirements of events and device deficiencies are outlined in Table 8.

Table 8: Adverse Event Reporting Requirements

Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE) and Unanticipated Adverse Device Effects (UADE):	
Investigator submit to:	**Sponsor submit to:**
Medtronic: Submit as soon as possible as per local reporting requirement, but not later than within 10 working days after the investigator first learns of the event. **Canada:** USADEs/SADEs on the patient, the user or any other person must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. Incidents that could lead to USADEs/SADEs, were it to reoccur, must also be reported within 72 hours. **In Europe:** Submit immediately (but no later than 10 working days) after the investigator learns of the event or of new information in relation with an already reported event. **In Japan:** Submit as soon as possible but no later than 3 business days after the designated study site personnel first learns of the event and to the IRB within the IRB required timeframe.	**Regulatory authorities (other than Australia):** Submit as soon as possible, but not later than within 10 working days after the Sponsor first receives notice of the event as per local reporting requirement. **In Australia:** Medtronic will adhere to the adverse event reporting requirements for Post Market Release (PMR) studies as per the requirements of the Therapeutic Goods (Medical devices) Regulations 2002. **In Canada**: Medtronic will adhere to the Medical Devices Regula-tions, SOR/98-282, Mandatory Problem Reporting Sections 59-61.
EC/IRB: Reporting timeframe as per local EC/IRB requirement.	**EC/IRB:** Reporting timeframe as per local EC/IRB requirement.
Serious Adverse Events (SAE)	
Investigator submit to:	**Sponsor submit to:**
Medtronic: Submit as soon as possible as per local reporting requirement, but not later than within 10 working days after the investigator first learns of the event. **Canada:** As required by Clinical Investigation Plan. **In Europe:** Submit immediately (but no later than 10 working days) after the investigator learns of the event or of new information in relation with an already reported event. **In Japan:** SAE must be reported by the investigator or delegated study staff to Medtronic within 24 hours after the investigator first learns of the event by completion of an AE eCRF page. If the eCRF database is not available or the site is unable to complete the eCRF due to technical reasons, the Sponsor should be notified of the event using a faxed SAE Rush Form. If the SAE is reported using a SAE Rush Form, an AE page of the eCRF should be completed within 3 business days after the designated investigational site personnel first learns of the event if possible.	**Regulatory authorities:** Reporting timeframe as per local requirement **In Japan:** All SAEs classified by Medtronic Japan Safety as reportable events will follow the applicable Pharmaceuticals and Medical Devices Agency (PMDA) reporting requirements (Ordinance for Enforcement of the Pharmaceutical and Medical Device Act, Article 274, paragraph 2). **In Australia:** Medtronic will adhere to the adverse event reporting requirements for PMR studies as per the requirements of the Therapeutic Goods (Medical devices) Regulations 2002.
EC/IRB: Reporting timeframe as per local EC/IRB requirement. **In Japan:** Upon reporting the SAE within 24 hours to Medtronic, the event must be reported to the site director (if required) by the investigator within the IRB required timeframe. **In Australia:** Report to the sponsor per local reporting requirements and without unjustified delay, all serious adverse events	**EC/IRB:** Reporting timeframe as per local EC/IRB requirement.
Adverse Device Effects (ADE)	
Investigator submit to:	**Sponsor submit to:**
Medtronic: Submit as soon as possible as per local reporting	**Regulatory authorities (other than**

Table 8: Adverse Event Reporting Requirements

requirement, but not later than within 10 working days after the investigator first learns of the event. **In Australia:** As required by Clinical Investigation Plan **In Europe:** Submit immediately (but no later than 10 working days) after investigator learns about new event or of new information related to an already reported event. **In Canada:** As required by the Clinical Investigation Plan	**Australia):** Reporting timeframe as per local requirement **In Australia:** Medtronic will adhere to the adverse event reporting requirements for PMR studies as per the requirements of the Therapeutic Goods (Medical devices) Regulations 2002.
EC/IRB: Reporting timeframe as per local EC/IRB requirement. **In Australia:** As required by EC .	**EC/IRB:** Reporting timeframe as per local EC/IRB requirement.
All other AEs	
Investigator submit to:	**Sponsor submit to:**
Medtronic: Submit as soon as possible as per local reporting requirement after the investigator first learns of the event. **In Australia:** As required by Clinical Investigation Plan **In Europe:** Submit in a timely manner after investigator learns about new event or of new information related to an already reported event.	**Regulatory authorities (other than Australia):** Reporting timeframe as per local requirement **In Australia:** Medtronic will adhere to the adverse event reporting requirements for PMR studies as per the requirements of the Therapeutic Goods (Medical devices) Regulations 2002.
EC/IRB: Submit to EC/IRB per local reporting requirement. **In Australia:** As required by EC **In Canada:** As required by the Clinical Investigation Plan	**EC/IRB:** Reporting timeframe as per local EC/IRB requirement.
Regulatory Authority: As per local reporting requirement.	
Device Deficiency with SADE potential	
Investigator submit to:	**Sponsor submit to:**
Medtronic: Submit as soon as possible as per local reporting requirement, but not later than 48 hours after the investigator first learns of the event. **In Europe:** Submit in a timely manner (but no later than 48 hours) after investigator learns about new event or of new information related to an already reported event. In **Canada:** DDs that have resulted in any of the consequences characteristic of an SADE on the patient, the user, or any other person, or could do so were it to reoccur, must be reported to the Sponsor within 72 hours after it comes to the attention of the qualified investigator.	**Regulatory authorities:** Reporting timeframe as per local requirement. **In Australia:** Medtronic will adhere to the adverse event reporting requirements for PMR studies as per the requirements of the Therapeutic Goods (Medical devices) Regulations 2002. In Canada: Medtronic will adhere to the Medical Devices Regulations, SOR/98-282, Mandatory Problem Reporting Sections 59-61.
EC/IRB: Reporting timeframe as per local EC/IRB requirement.	**EC/IRB:** Reporting timeframe as per local EC/IRB requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit as soon as possible as per local reporting requirement, but not later than 48 hours after the investigator first learns of the event. **In Europe:** Submit in a timely manner (but no later than 48 hours) after investigator learns about new event or of new information related to an already reported event. **In Canada:** As required by the Clinical Investigation Plan
Regulatory Authority	As per local reporting requirement

Table 8: Adverse Event Reporting Requirements

EC/IRB	Submit to EC/IRB per local reporting requirement.

F.16.5 Data Safety Monitoring Board and Clinical Events Committee

A Data Safety Monitoring Board (DSMB) will be established to monitor the health, safety and welfare of patients. Additionally, a Clinical Events Committee (CEC) will be established to adjudicate any safety endpoint events. See Section I.2 Advisory Committees.

F.16.6 Emergency contact details in case of serious AEs

In the case a Serious Adverse Event or Serious Adverse Device Effect occurs and requires immediate consultation, the investigators can contact the sponsor (or designee) as outlined in the Investigator Site File.

F.17 Subject accountability

F.17.1 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 F.17. 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.

F.17.2 Unscheduled Follow-up Visits

If a subject returns to the institution between the protocol-required screening or follow-up visits for one of the following reasons: an escape medication change, evaluating subjects during medication re-introduction, repeat procedures (serum creatinine blood draw, ABPM, renal imaging), re-consenting, or drug testing for elevated blood pressure resulting in a hospitalization or emergency room visit, 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 eCRF and AE data on the Unscheduled AE eCRF (if applicable). If the subject returns for another reason, this will not need to be documented.

F.17.3 Subject Withdrawal or Lost To Follow-up

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. 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 his/her status outside the clinical study.

F.17.4 Subject Exit From Study

There are many scenarios in which a subject may exit the study. Table 9 details how the data will be handled for each scenario.

Table 9: 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 (not randomized)	None
Subject enrolled, randomized 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, randomized and completes the study requirements	Through 3 year follow-up
Subject enrolled, randomized but has an office SBP ≥180 mmHg or is put back on medications before 3 months post-procedure	Through 3 year follow-up
Subject enrolled, randomized, completed crossover procedure and completes the study requirements	Through 2 year follow-up

F.18 Study deviations and CIP changes

A study deviation is an event where the investigator or investigational site personnel did not conduct the clinical study according to the Clinical Investigation Plan or Clinical Study Agreement. The investigator is not allowed to deviate from the above mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

Medtronic will assess the significance of all deviations and evaluate the need to amend the Clinical Investigation Plan or to early terminate the investigation, in accordance with Medtronic SOPs.

F.18.1 Request for approval of study deviations

The investigator shall obtain documented approval from Medtronic, before implementation, for any change in- or deviation from the Clinical Investigation Plan. In case of study deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical study, approval from the EC/IRB and regulatory authority must also be obtained before implementation. The investigator shall contact the Clinical Study Manager for review of the proposed change/deviation.

Prior approval is not always possible in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation, and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the Clinical Investigation Plan do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to

Medtronic and the reviewing EC/IRB, if applicable. Medtronic will inform the regulatory authorities, if required.

F.18.2 Reporting requirements for study deviations

For reporting purposes Medtronic classifies deviations as major or minor protocol (Clinical Investigation Plan) deviations. Major protocol (Clinical Investigation Plan) deviations are deviations with respect to inclusion/ exclusion criteria and no patient informed consent prior to study procedures.

Deviations will be recorded at the site and reported to Medtronic on the eCRF. The deviation document shall be signed and dated by the investigator or his authorized designee. At a minimum the following information will be recorded:

- identification of the investigator and site
- description of deviation
- date of occurrence
- reason for the deviation
- patient identifier, if associated with the event

Deviations will be entered into a database to allow a comprehensive review on a regular basis for identifying trends that warrant additional preventive or corrective actions to mitigate further occurrence. Clinical study management at Medtronic shall conduct this review.

Study deviations must be reported to Medtronic, regardless of whether medically justifiable, pre-approved by the study leader (see contact details section), or taken to protect the subject in an emergency. In the case that the deviation involves a failure to obtain a subject's informed consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the EC/IRB as well as the study leader as soon as possible after the occurrence of the event. Reporting of all other study deviations should comply with EC/IRB policies and/or local laws.

The investigator shall adhere to EC/IRB requirements and procedures for reporting study deviations.

The clinical study team shall provide regular site-specific reports to the investigator(s) summarizing information on deviations that occurred at the investigational site. The frequency of these reports will depend on the stage in the study and number and details of protocol deviations.

All deviations from the CIP shall be included in the final report.

Specific examples of study deviations are, but not limited to:

- failure to obtain the Patient Information and Informed Consent Form prior to participation
- incorrect version of the Patient Information and Informed Consent Form used
- no EC/IRB approval before the start of the study
- enrolled patient did not meet inclusion/exclusion criteria
- randomization processes not followed
- CIP required testing and/or measurements not done or incorrectly done
- patient did not attend follow up visit or follow up visit outside window

- Adverse Events not reported by investigators in the required time frame as specified in the CIP
- source data permanently lost
- enrollment of patients 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.

F.18.3 Amendments to the Clinical Investigation Plan

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

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their EC/IRB. The investigator will only implement the amendment after approval of the EC/IRB, regulatory authority and sponsor. Administrative amendments to the Clinical Investigation Plan will be submitted to the EC/IRB for notification. Furthermore, investigators shall sign any approved amendment for agreement.

G QUALITY CONTROL PROCEDURES

G.1 Procedures for database management

G.1.1 Data collection

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 patient medical file.

Only authorized persons can complete CRFs. CRFs shall be signed and dated 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.

G.1.2 Source data to be directly recorded on the 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).

The eCRFs (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.

G.1.3 Time windows for completion and submission of Case Report Forms

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

G.1.4 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 the data.

G.2 Monitoring procedures

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. 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.

A site initiation visit will be performed to prepare the site and it may include training and collection of the required documentation, such as Curricula Vitae. Monitors will verify whether signed and dated patient Information, if applicable, and informed consent forms have been obtained from each subject at the point of enrollment before any study procedure has been performed.

Specific monitoring requirements are detailed in the monitoring plan. In order to ensure a high degree of data quality, all enrolling clinical centers will be monitored frequently. The aim is to monitor the source data of minimally 90% of data collected in the study. In addition, the aim, is to verify all available informed consent forms of enrolled patients at the center during the monitoring visits. The principal investigator should be available during monitoring visits.

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

For the duration of the study, Medtronic or designee will conduct site monitoring visits to assess, A) compliance with the protocol, clinical trial agreement, and applicable regulations, B) adherence to the data collection procedures, C) accuracy and completeness of submitted clinical data, and D) proper maintenance of records.

Monitoring activities will be documented, including a summary of items 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 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 will be conducted by Medtronic's technical support staff on an annual basis.

In Japan, monitors follow the Japan GCP Ordinance to ensure compliance with the study protocol and Good Clinical Practice for Medical Devices.

G.2.1 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 Case Report Form (CRF). Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

G.2.2 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. Independent 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.

G.3 Study suspension or early termination

Termination of the study is discontinuance, by sponsor or by withdrawal of IRB/EC or local regulatory body approval, or 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 is study suspension or early termination, it is up to

the investigator's discretion to assess whether or not to continue the clinical study at the respective investigational site.

G.3.1 Early study suspension or termination

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

G.3.2 Early investigation site suspension or termination

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

- Failure to obtain initial IRB/EC 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.)
- IRB/EC 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)

G.3.3 Procedures for planned study closure, termination or suspension

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).

G.3.3.1 Medtronic-initiated

- In the case of study termination or suspension for reasons other than a temporary IRB/EC approval lapse, the investigator will promptly inform the IRB/EC.
- 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.

G.3.3.2 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 IRB/EC.
- 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.

G.3.3.3 IRB/EC-initiated

- The investigator will promptly inform:
  - Medtronic and provide a detailed written explanation of the termination or suspension within 5 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 IRB/EC suspension is lifted.
  - Subjects already enrolled should continue to be followed in accordance with IRB/EC policy or its determination that an overriding safety concern or ethical issue is involved.

G.3.4 Criteria for unblinding

Reasons for unblinding are:

- All randomized patients will be unblinded during the 6 month follow-up visit. The procedure will be offered to the randomized Control patients that continue to meet eligibility criteria after this visit.
- All randomized patients will immediately be unblinded in case of study termination.
- When a site is terminated, all randomized patients of this site will immediately be unblinded.

Unblinding must be documented including the signature of site study personnel, date and reason for unblinding and must be reported to the Clinical Study Manager. The unblinding will be documented on a separate file that can be found in the ISF.

G.4 Study close out

Upon study completion or termination Site Closeout Visits will be conducted, as outlined in the Monitoring Plan. After the study has been completed or terminated, medical care will be provided to the subjects upon the discretion of the treating physician.

In Japan, upon completion of the clinical study (when enrollment of all prospective subjects has been completed, all follow-up visits have been completed and data queries resolved and all eCRFs have been approved), the investigator will notify the institution director of the site closeout. Medtronic Japan will submit a clinical study notification to the regulatory authority at the time of study close-out.

H DATA ANALYSIS AND REPORTING

Any deviations from this section and/or the Statistical Analysis Plan will be described and justified in the Final Clinical Study Report, as appropriate or justified in the CIP, if applicable.

H.1 Analysis of clinical data

General Analysis Overview

Descriptive statistics of continuous outcomes will be presented by treatment arm and include sample size, mean, median, standard deviation, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented by treatment arm. Statistical comparisons between treatment arms will be made using t-tests for continuous outcomes and chi-square or Fisher's exact test (depending on overall event rates) for categorical outcomes. Paired t-tests will be used to compare changes from baseline to follow-up within each treatment arm. All statistical analyses will be performed using SAS for Windows (version 8.2 or higher) or other widely accepted statistical or graphical software. Patient data listings and tabular and graphical presentations of results will be provided. Unless otherwise specified, a two-sided 0.05 level of significance will be used to declare treatment arms significantly different. Additional details on the analysis will be provided separately in the SPYRAL HTN OFF-MED Statistical Analysis Plan (SAP) for this study.

H.1.1 Analysis Sets

a. Intent-to-Treat (ITT): All randomized subjects, analyzed according to their randomized treatment. Subjects who meet the antihypertensive medication escape criteria (OSBP>180 or safety reasons) will be analyzed using Last Observation Carried Forward (LOCF) for their blood pressure measurements.

b. Modified Intent-to-Treat : All randomized subjects, analyzed according to their randomized treatment. Subjects who meet the antihypertensive medication escape criteria (OSBP>180 or safety reasons) will be excluded from this population.

c. Per-Protocol (PP): All randomized subjects, meeting the following criteria:

    1. Subjects showing medication compliance in blood and/or urine (via drug testing data) at SV2 and 3M

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 mm Hg and <180 mm Hg and an office DBP ≥ 90 mm Hg measured at Screening Visit 2, according to the guidelines in Appendix L7.

   - Inclusion: Individual has a 24-hour ABPM average SBP ≥140 and < 170 mm Hg measured at Screening Visit 2, according to guidelines in Appendix L7.

   - 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 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.

4. Exclude subjects meeting the antihypertensive medication escape criteria (OSBP>180 or safety reasons).
5. Exclude subjects who did not receive the treatment they were randomized to.

d. As Treated Population: All randomized subjects, analyzed according to the actual treatment received. Subjects randomized to RDN who do not get treated will be analyzed in the control arm. Subjects who meet the anti-hypertensive medication escape criteria will be analyzed using Last Observation Carried Forward (LOCF) for their blood pressure measurements out to 3 months.

H.2 Primary Safety Objective

Medtronic is using a performance goal approach to analyze the primary safety endpoint. The safety performance goal for the Major Adverse Event (MAE) rate was developed based on review of and comparison to event rates of other renal interventions. The reported events differed among the studies; however, for a subset of these studies, we could estimate rates for a composite of events similar to our protocol's MAE composite. The major adverse event rate from these studies was 7.1% which will be used as the performance goal for the primary safety endpoint. Additional details on the performance goal calculation can be found in the SAP.

The primary safety null and alternative hypotheses are:

H_0: $\pi \geq 7.1\%$ vs.

H_a: $\pi < 7.1\%$

where π is the MAE rate for patients undergoing renal denervation. Under the assumption that the true rate is 3.5%, and using a one-sided 0.05 level of significance, an evaluable sample size of 253 renal denervation patients yields 80% power to reject the null hypothesis in favor of the alternative. The exact binominal test was used for the sample size calculation for the primary safety endpoint hypothesis.

In other words, the primary safety endpoint hypothesis is designed to show whether the true MAE rate is lower than 7.1%. Compared to the literature reported event rates for renal intervention, it is believed that these thresholds are appropriate for demonstrating safety of the device given the expected performance rates of similar renal intervention trials, particularly when balanced with the expected blood pressure reductions.

Medtronic proposes multiple sources of study subjects as shown in Table 10 below to ensure 253 patients treated with the Symplicity Spyral catheter (including branch treatment) are available for analysis. The first consecutively randomized 253 subjects with evaluable safety data from the sources in Table 10 will be used to perform the primary safety endpoint analysis.

With a sample size of 253 and a one-sided significance level of 0.05, a maximum of 11 subjects with MAE will enable us to meet the safety primary endpoint, resulting in an event rate of 4.3% with a one-sided 95% upper confidence bound of 7.09% using the exact binomial method.

Table 10 Study Sources of Patients for Primary Safety Endpoint Data

Study
SPYRAL HTN-OFF MED (First 80 Subjects) Randomized 1:1 to RDN:Control
SPYRAL PIVOTAL – SPYRAL HTN-OFF MED Randomized 1:1 to RDN:Control
SPYRAL HTN-ON MED (First 106 Subjects) Randomized 1:1 to RDN:Control
SPYRAL HTN ON MED Extension Randomized 2:1 to RDN:Control
SPYRAL HTN-OFF MED Crossovers (from first 80 subjects and Pivotal)
SPYRAL HTN-ON MED Crossovers

H.3 Secondary Safety Objectives

The following secondary safety endpoints will be assessed:

- Acute/Procedural Safety Secondary Endpoints – Compared Between Groups at 1 Month Post-Procedure:
    - Significant embolic event resulting in end-organ damage
    - Renal artery perforation requiring intervention
    - Renal artery dissection requiring intervention
    - Vascular complications
    - End-Stage Renal Disease
    - ≥40% decline in eGFR
    - New Myocardial Infarction
    - New Stroke
    - Renal artery re-intervention
    - Major bleeding according to TIMI definition (i.e. intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)
    - Increase in serum creatinine > 50% from Screening Visit 2
    - New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core laboratory
    - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol.

- Chronic Safety Secondary Endpoints – Compared Between Groups at 3, 6, 12, 24, and 36 Months Post- Randomization:
    - All-cause mortality
    - End-Stage Renal Disease
    - ≥40% decline in eGFR

- New Myocardial Infarction
- New Stroke
- Renal artery re-intervention
- Major bleeding according to TIMI definition (i.e. intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)
- Increase in serum creatinine > 50% from Screening Visit 2
- Renal artery stenosis >70%, confirmed by angiography
- Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol.

All the safety endpoints will be adjudicated by the Clinical Events Committee (CEC). The following algorithm will be used to evaluate the safety event rates: The denominator will include all subjects who either had a CEC adjudicated event prior to the time of interest (180 days for 6 months events, for example), or had last contact date that is beyond the lower window of the follow up (166 days for 6 month events, for example). The numerator will include all subjects who had CEC adjudicated events up to the time of interest (180 days for 6 months events, for example). The secondary safety endpoints will be compared between treatment groups using Fisher's exact test. In addition, two-sided 95% confidence intervals of the difference between treatment groups will be presented. The secondary safety analyses will be performed using the ITT population defined in H1.

H.3.1 Renal Artery Stenosis Evaluation at 12 Months

With the expected rate of 3.1% for stenosis at 12 months[41], a sample size of 100 subjects will provide a 95% confidence interval of approximately (0.6%, 8.5%) using the exact method (calculated using an event rate of 3/100=3%).

Descriptive statistics of this endpoint at 12 months will be provided using counts, percentages and the 95% confidence interval.

H.4 Primary Efficacy Objective

The primary efficacy endpoint of the study is the baseline adjusted (analysis of covariance/ANCOVA) change in SBP from baseline (screening visit 2) to 3-months post-procedure as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM).

In the context of an ANCOVA linear regression model, $\mu = \mu_t - \mu_c$ represents the baseline-adjusted treatment effect of BP change comparing test and control groups where μ_t and $\mu_c$are the baseline adjusted BP changes in the denervation and control arms respectively. Let $y =$

$\{y_t, y_c\}$ and $y_0 = \{y_{0t}, y_{0c}\}$represent the current data and historical data respectively, where $t =$ test group and $c =$ control group. Let the hypotheses for the study be the following :

$$H_0: \mu = 0$$

$$H_a: \mu < 0$$

We reject H_0 if the probability is greater than 97.5%, i.e.

$$P(\mu < 0 | y, y_0, \widehat{\alpha_0}(y, y_0, \lambda, k)\ ) > 0.975$$

where the notation $\widehat{\alpha_0}(y, y_0, \lambda, k)$ is used to denote that the estimate of $\widehat{\alpha_0}$ depends on the current data, prior data, and the Weibull shape and scale parameters. In conjunction with a pre-specified decision rule controlling the prior data weight, the estimate of $\widehat{\alpha_0}(y, y_0, \lambda, k)$ represents a measure of similarity between current current and prior data. Alternatively, in the absence of $\widehat{\alpha_0}(y, y_0, \lambda, k)$, i.e., $P(\mu < 0 | y, y_0)$, full weight would be given to the prior data.

The power prior discount function approach is used to estimate μ, and determine $\widehat{\alpha_0}(y, y_0, \lambda, k)$, the strength of the historical data used to estimate μ. $\widehat{\alpha_0}(y, y_0, \lambda, k)$ ranges from 0 to 1, where 1 means that 100% of the historical data is used and 0 means that no historical data is used. Before beginning the study, an initial value is chosen for $\widehat{\alpha_0}(y, y_0, \lambda, k)$, call this value α_{max}. This α_{max} value is the maximum strength the historical data can receive. The intend to use the same enrollment criteria for the prior and pivotal studies, and therefore believe that a value of $\alpha_{max} = 1$ is appropriate.

At interim looks and at the final analysis, we analyze the data using the power prior discount function method, this method will discount α_{max} to an appropriate value $\widehat{\alpha_0}(y, y_0, \lambda, k)$ where $\widehat{\alpha_0}(y, y_0, \lambda, k) \leq \alpha_{max}$. This discounting is based on the discount function which is discussed in more detail in the SAP. Under the adaptive procedure, if the current data diverges from the historical data at an interim look, the discount function will discount the strength of the historical data, thus requiring continued enrollment to maintain power to achieve the endpoint. Alternatively, if the historical and current data agree, there will be a smaller penalty from the discount function, thus fewer prospective patients would be needed to maintain power, and enrollment may stop early. A more detailed formulation of the efficacy endpoint analyses can be found in the Statistical Analysis Plan.

The ITT population defined in section H1 will be used as the primary analysis population for this endpoint. Secondary effectiveness analyses will also be performed using the modified ITT per-protocol and as-treated populations.

H.5 Secondary Efficacy Objective

The secondary powered efficacy endpoint is the baseline adjusted change in office SBP from baseline (screening visit 2) to 3-months post procedure, compared between treatment arms.

In the context of an ANCOVA linear regression model, $\mu = \mu_t - \mu_c$ represents the baseline-adjusted treatment effect of BP change comparing test and control groups where μ_t and μ_c are the baseline adjusted BP changes in the denervation and control arms respectively. Let

$y = \{y_t, y_c\}$ and $y_0 = \{y_{0t}, y_{0c}\}$ represent the current data and historical data respectively, where the subscripts t = test group and c = control group. Let the hypotheses for the study be the following:

H_0: $\mu = 0$

H_a: $\mu < 0$

We reject H_0 if the probability is greater than 97.5%, i.e.

$$P(\mu < 0 | y, y_0, \widehat{\alpha_0}(y, y_0, \lambda, k)\ ) > 0.975$$

where the notation $\widehat{\alpha_0}(y, y_0, \lambda, k)$ is used to denote that the estimate of $\widehat{\alpha_0}$ depends on the current data, prior data, and the Weibull shape and scale parameters. In conjunction with a pre-specified decision rule controlling the prior data weight, the estimate of $\widehat{\alpha_0}(y, y_0, \lambda, k)$ represents a measure of similarity between current current and prior data. Alternatively, in the absence of $\widehat{\alpha_0}(y, y_0, \lambda, k)$, i.e., $P(\mu < 0 | y, y_0)$, full weight would be given to the prior data.

A more detailed formulation of the efficacy endpoint analyses can be found in the SAP.The same statistical methods as outlined in section H4 will be used to analyze the powered secondary endpoint. The ITT population defined in section H1 will be used as the primary analysis population for this endpoint. Secondary effectiveness analyses will also be performed using the modified ITT population and per-protocol populations.

H.5.1 Simulation of Primary and Secondary Efficacy Endpoint Operating Characteristics

As outlined in section B.6, enrollment will be stopped at an interim analysis for efficacy or futility only if both the primary and secondary efficacy endpoints meet the stopping criteria. Simulations were performed to assess operating characteristics for the primary and secondary efficacy endpoints. We used 8000 trial simulations to estimate the power and 15000 simulations to estimate the type I error. Tables 11 and 12 summarize the assumptions that were made for the primary and secondary efficacy endpoint simulations, and table 13 summarizes the operating characteristics for the efficacy evaluation. The overall power for the efficacy evaluation from table 13 is 94%, with a one-sided type I error rate of 0.026 for 24-hour SBP and 0.028 for Office SBP.

Table 11: Simulation Assumptions for Primary Efficacy Endpoint

Enrollment Rate	10 Subjects / Month
Prior Baseline Adjusted Treatment Arm Mean/SE	-5.30 / 1.65 mmHg
Prior Treatment Arm N	35
Prior Baseline Adjusted Control Arm Mean/SE	-0.74 / 1.62 mmHg
Prior Control Arm N	36
Maximum Prior Patients	35 RDN + 36 Control = 71
Pivotal Study Expected Treatment Difference	4.0 mmHg
Pivotal Study Treatment Arm Mean/SD	-4.74 / 12 mmHg
Pivotal Study Control Arm Mean/SD	-0.74 / 12 mmHg

Weibull Discount Function Parameters	Shape: $k = 3$, Scale: $\lambda = 0.5$

Table 12: Simulation Assumptions for Secondary Efficacy Endpoint

Enrollment Rate	10 Subjects / Month
Prior Baseline Adjusted Treatment Arm Mean/SE	-9.69 / 2.20 mmHg
Prior Treatment Arm N	37
Prior Baseline Adjusted Control Arm Mean/SE	-2.54 / 2.09 mmHg
Prior Control Arm N	41
Maximum Prior Patients	37 + 41 = 78
Pivotal Study Expected Treatment Difference	6.5 mmHg
Pivotal Study Treatment Arm Mean/SD	-9.04 / 16 mmHg
Pivotal Study Control Arm Mean/SD	-2.54 / 16 mmHg
Weibull Discount Function Parameters	Shape: $k = 3$, Scale: $\lambda = 0.5$

Table 13: Operating Characteristics for Primary and Secondary Efficacy Endpoints

Trial Success Rate (Power)	94%
Type I Error (one-sided)	24-Hr SBP: 0.029 Office SBP: 0.026
First Interim Look N	N=210
Power at First Interim Look	83%
Second Interim Look N	N=240
Power at Second Interim Look	89%
Maximum Study Size	N=300
% of Simulations that Stop for Futility	0.05%

H.6 Other Secondary Efficacy Endpoints

The following additional secondary efficacy endpoints will be assessed:

- Change in systolic blood pressure (SBP) from baseline (Screening Visit 2) as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM) at 3, 6, 12, 24 and 36 months post-procedure.
- Change in office systolic blood pressure from baseline (Screening Visit 2) at 1, 3, 6, 12, 24 and 36 months post-procedure.
- Incidence of achieving target office systolic blood pressure (SBP <140 mmHg) at 1, 3, 6, 12, 24 and 36 months post-procedure.
- Change in office diastolic blood pressure from baseline (Screening Visit 2) at 1, 3, 6, 12, 24 and 36 months post-procedure.

- Change in diastolic blood pressure from baseline (Screening Visit 2) as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM) at 3, 6, 12, 24 and 36 months post-procedure.

The efficacy endpoints will be compared between treatment groups using t-tests for continuous endpoints and Fisher's exact test for categorical endpoints. In addition, two-sided 95% confidence intervals of the difference between treatment groups will be presented. Changes in blood pressure measurements from baseline to follow-up within each treatment group will be assessed using paired t-tests. Two-sided 95% confidence intervals of the mean change from baseline will be presented for each treatment group.

Analysis of Covariance (ANCOVA) models, adjusting the treatment effect for the baseline BP measurements will also be presented.

These additional efficacy analyses will be presented for all the study populations defined in section H1.

H.7 Additional Objectives

The following additional analyses will be conducted:

- Quality of Life (QOL) measures (EQ5D and SF36)
- Antihypertensive medication usage through 36 months.
- Additional procedural characteristics e.g. treatment duration, frequency of distal renal artery treatment, ablations per vessel, location of ablations, number of ablations per patient and other characteristics will be analyzed to assess their impact on blood pressure.
- In accordance with FDA guidance document "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" [8], we will provide AE and SAE tables summarizing the site-reported adverse events attributed to COVID-19.

Descriptive statistics will be presented by treatment arm. Statistical comparisons between treatment arms will be made using t-tests for continuous outcomes and Fisher's exact test for categorical outcomes.

These additional analyses will be presented for the ITT study population defined in section G1.

H.8 Safety Evaluation

Adverse Event (AE) information will be collected by the site from subject enrollment (consent) through study termination. 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.

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 or not 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.

H.9 Subgroup Analyses

Analysis will be carried out for the following subgroups to assess consistency of results.

- Gender
- Age at baseline <65 vs. ≥ 65 (years)
- BMI by tertiles (kg/m2)
- Type 2 diabetics vs. non-diabetics
- Current smokers vs. non-smokers
- Baseline eGFR < 60 vs. ≥ 60 (mL/min/1.73 m2)
- Obstructive sleep apnea yes vs. no
- US vs. OUS Subjects
- US African American vs. US Non African American subjects
- European vs. Japanese vs. Australian subjects
- Baseline ambulatory SBP by tertiles and medians (mmHg)
- Baseline office SBP by tertiles and medians (mmHg)
- Baseline ambulatory heart rate by tertiles and medians (bpm)
- Baseline office heart rate by tertiles and medians (bpm)
- 24-Hour Pulse Pressure <60 vs. >= 60 mmHg (mmHg)
- Orthostatic Hypertension at baseline
- Orthostatic Tachycardia at baseline
- Plasma Renin Activity at baseline <0.65 vs. ≥0.65 (ng/mL/h)
- Aldosterone Renin Ratio at baseline by tertiles
- Aldosterone at baseline by tertiles (ng/dL)
- Tertile analysis by total number of ablations performed
- Tertile analysis by total number of ablations performed in branch vessels
- Tertile analysis by total number of ablations performed in main renal artery vessels
- Tertile analysis by total number of 45 second ablations performed
- Medication adherent vs. non-adherent subjects at screening visit 2 (SV2) and 3 months (from urine and serum tests)

H.10 Publication Policy

Medtronic may form a Publications Review Committee. Member(s) of the Publications Review Committee may include, but are not limited to, the Executive Steering Committee, the Medtronic Clinical Study Manager or Publication Manager, and other Medtronic personnel.

Participating investigators and members of the Executive Steering Committee 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[21] and GPP2 guidelines[22] 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.

I STUDY MANAGEMENT

I.1 Study staff

A list of sponsor staff (including sponsor's medical expert(s), suppliers, and core labs for this trial along with their contact information (i.e., name, title, address, and telephone number(s)) will be provided separately and will be maintained within the study files at each site.

I.2 Advisory committees

I.2.1 Executive Steering Committee

The Executive Steering Committee is comprised of the Study Coordinating Investigators and selected members of Medtronic. Additional individuals may be consulted as appropriate. The main responsibilities of the Executive Steering Committee are to provide oversight and general guidance for the global study design and execution, to define the primary publication plan, and to prioritize publication requests and approvals.

The Executive Steering Committee will meet periodically by teleconference and in-person to discuss patient enrollment and clinical site progress, as well as generally assist sites with the successful conduct of the study. The Executive Steering Committee will be responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications.

I.2.2 Data Safety Monitoring Board (DSMB)

The primary responsibility of the Data Safety Monitoring Board (DSMB) is to monitor the health, safety and welfare of patients. 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 studies. 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 patients 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 trial 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.

I.2.3 Clinical Events Committee (CEC)

The primary responsibilities of the Clinical Events Committee (CEC) 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. The members of the CEC will not be investigators in the study or members of the DSMB and will be independent of Medtronic.

During the first CEC meeting guidelines for the AE adjudication process will be established. Additional details on the definitions utilized for adjudication, the adjudication process as well as reporting of outcomes will be provided in the CEC Charter. The proceedings of each CEC meeting will be recorded in minutes.

Medtronic personnel may attend the meetings to answer questions but will not have a vote in determining the committee's recommendations. The Medtronic Safety Department will identify safety events meeting criteria for review by the CEC. They will provide this information based upon the established rules of the CEC. The CEC will meet regularly to review and adjudicate all events in which the required minimum data are available.

I.2.4 Publications Review Committee

Member(s) of the Publications Review Committee may include, but are not limited to, the Executive Steering Committee, the Medtronic Clinical Study Manager or Publication Manager, and other Medtronic personnel. As this committee represents the Medtronic Global Renal Denervation Program and may not be study-specific, there is no specific timeframe for this

committee to disband. See Section G10 Publication Policy for details on the activities of this committee.

I.3 Records and reports

I.3.1 Investigator records

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

- Medtronic and EC/IRB Clinical Investigation Plan 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
- Subject Enrollment 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
- Completed Delegated Task List and Curriculum Vitae of all investigation site personnel
- Training documentation of all investigation site personnel
- Relevant communications

- Subject screening log and/or subject identification log
- Signed, dated and fully executed Patient Information and Informed Consent Form
- Fully executed eCRFs and corrections
- Reports of Adverse Events and Device Deficiencies
- Device and drug accountability records
- Randomization list and randomization forms
- 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
- Randomization list and randomization documentation
- List of investigational sites
- Any other records that may be required by hospital regulations or local law

I.3.2 Investigator reporting responsibilities

Report	**Submitted to**	**Description**
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 5 working days of the investigator's part of the investigation.
Final Clinical Study Report	EC/IRB (all sites), Sponsor (US sites)	○ A copy of the Final Clinical Study Report will be provided to the EC/IRB. The report will be submitted to the local EC/IRB in accordance with the EC/IRB policies and procedures. ○ In the US, the final report must also be submitted to the Sponsor within 3 months after termination or completion of the investigation or the investigator's part of the investigation.
Deviations from Clinical Investigational Plan		
Emergency Use	Sponsor, EC/IRB, regulatory authority	Investigator will report deviation as soon as possible to the sponsor and EC/IRB.

Report	Submitted to	Description
Planned deviation	Sponsor, EC/IRB, regulatory authority	Prior approval 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 regulatory authority.
Other Deviations	Sponsor	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.

I.3.3 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
- 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 Informed Consent Forms
- Site visit reports
- Adverse event and Device Deficiency reports
- Financial disclosure information
- Fully executed CRFs and corrections
- Randomization list and randomization forms

I.3.4 Sponsor reporting responsibilities

Report	**Submit to**	**Description**
Withdrawal of EC/IRB 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.
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.

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 Clinical Investigational Plan	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.

I.3.5 Record retention

The investigator must retain the Investigator Site File, patient medical files and CRFs in accordance with local law and regulations for a minimum period of 2 year (or longer if local laws require) after market-release in his/her region. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

In Japan, investigational sites must retain all study-related documents until the later date of the time points below:

- Day of marketing approval of the investigational device (day 3 years from the date of the decision to discontinue development when notification that development will be discontinued pursuant to the provisions of the J-GCP Ordinance has been received)
- 3 years from the date of termination or closure of the clinical study

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 in accordance with J-GCP and Medtronic policy.

I.4 Miscellaneous

I.4.1 Insurance

Medtronic, Inc. (including all wholly owned subsidiaries) 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.

I.4.2 Subject compensation and indemnification

Subjects will not receive any compensation for their participation in this study. Medtronic will provide subject indemnification according to local laws where this study will be conducted and as outlined in the Clinical Study Agreement.

I.4.3 Subject confidentiality

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 patient study ID and an individual patient. 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.

In the United States, "Protected Health Information" (PHI) will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the informed consent form, as required by EN ISO5840: 2009. This scenario will be covered in the Patient Information-Informed Consent Form. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel.

In geographies outside the United States, investigational sites will protect the personal information of subjects in accordance with national, local and 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.

J RISKS AND BENEFITS

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 patients 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[23,24], with large individual patient 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, patients 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 patient 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 patients, physicians and the health system.

J.1 Anticipated Clinical 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 patients 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 patients with either severe hypertension or heart failure[25]. 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 patients with heart failure[26-30]. 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.[31]

Reduction of central sympathetic activity may also reduce resistance to the action of insulin – potentially improving glycemic control.[32,33]

There are no guaranteed benefits from participation in the study.

J.2 Risks

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):

- Death – a complication or deterioration of health ultimately leading to a patient'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 6 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 3 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 magnetic resonance imaging (MRA) or computerized tomographic angiography (CTA). The risks of undergoing an MRA include: medication patches can cause a skin burn, claustrophobia from being enclosed within the MRA magnet, and allergic reaction to the contrast material (if used). The presence of implanted metal devices may be a contraindication to undergoing MRA due to heating, movement, or disruption of programming of electronic devices. Nephrogenic systemic fibrosis (NSF) may occur when Gadolinium is administered to subjects with reduced eGFR. 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 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.

J.3 Minimization of Risk

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 clinical investigation plan:

1. 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 patient management and monitoring, Symplicity Spyral™ catheter delivery and RF ablation, and post-procedural care.

2. *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.

3. The system's design and software include several safety mechanisms to reduce risk to the patient (limitations on temperature, time, impedance, and power delivered to the subject).

4. Subjects will be closely monitored by appropriately trained personnel during the procedure and at regularly scheduled intervals for the duration of the study.

5. Physicians will employ usual and customary clinical technique (e.g., sterile technique during catheter use and aseptic wound care procedures).

6. A Data Safety Monitoring Board (DSMB) will be established to monitor the health, safety and welfare of patients 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.

J.4 Risk-to-Benefit Rationale

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.

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L APPENDICES

L.1 Names and addresses

L.1.1 List of contact persons

Coordinating investigator

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

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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.

Service Provider	Contact Information	Services	Scope and Duties Entrusted
Medtronic, Inc. (Global Sponsor)	3576 Unocal Place Santa Rosa, CA 95403 USA	Monitoring Data Management Statistical Programming and Data Analysis	Medtronic is responsible for the source data verification and compliance with the study Clinical Investigation Plan and applicable regulations (Monitoring); review and cleaning of the data (Data Management) and statistical programming and data analysis.
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.
ACM Global Laboratory	160 Elmgrove Park Rochester, NY 14624 USA	Blood Core Laboratory	Blood Core Lab is responsible for processing and analyzing test samples for renin and aldosterone.

Service Provider	Contact Information	Services	Scope and Duties Entrusted
ICON Clinical Research	2800 Kelly Road Suite 200 Warrington, PA 18976 USA	Central Registration and Randomization Center	The Central Registration and Randomization Center will be responsible for developing and maintaining the randomization system for the study.
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 patients. 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 antihypertensive 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.
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.
Cytel		Statistical Programming and Data Analysis	Independent statistical data analysis and validation

L.1.2 List of participating investigational sites and investigators

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

L.2 Case Report Forms

A copy of the Case Report Forms will be provided under a separate cover.

L.3 Sample Investigator Agreement

A sample Investigator Agreement will be provided under a separate cover.

L.4 Abbreviations

ABPM Ambulatory Blood Pressure Monitoring
ADE Adverse Device Effect
AE Adverse event
AF Atrial fibrillation
BP Blood pressure
BPM Beats per minute
CEC Clinical Events Committee
CIP Clinical Investigation Plan
CRF Case Report Form
CRO Clinical Research Organization
DD Device Deficiency
DSMB Data Safety Monitoring Board
DUS Duplex Ultrasound
EC Ethics Committee
eCRF Electronic Case Report Form
eGFR estimated Glomerular Filtration Rate
EDC Electronic Data Capture
FDA Food and Drug Administration
FU Follow up
ICH-GCP International Conference on Harmonization – Good Clinical Practice
IDE Investigational Device Exemption
IRB Institutional Review Board
MRA Magnetic Resonance Angiography
OBP Office Blood Pressure
PMDA Pharmaceuticals and Medical Devices Agency
SADE Serious Adverse Device Effect
SAE Serious Adverse Event
SOP Standard operating procedure
TGA Therapeutic Goods Administration

L.5 Definitions

Event definitions:

- Major Adverse Events (MAE), defined as a composite of the following events, compared between groups:

  o All-cause mortality

  o End-stage Renal Disease (ESRD) – defined as two or more eGFR measurements < 15 mL/min/1.73m^2 at least 21 days apart and requiring dialysis for one of 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

  o 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)

  o Renal artery perforation requiring intervention

  o Renal artery dissection requiring intervention

  o Vascular complications (e.g., clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm, excessive bleeding) requiring surgical repair, interventional procedure, 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 renal denervation procedure)

  o Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications. Hypertensive Crisis: Severely elevated blood pressure (BP), usually higher than 180/110 mmHg, 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 non-adherence with medication or the protocol.

  o New renal artery stenosis > 70%, confirmed by angiography by the angiographic core lab

- Major bleeding according to TIMI definition (i.e. intracranial hemorrhage; ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)

Estimated Glomerular Filtration Rate (eGFR) calculation method for Japanese: eGFR (mL/min/1.73 m^2) = 194 x $(sCr)^{-1.094}$× $(Age)^{-0.287}$ x (0.739 if female)

L.6 Center for Medicare and Medicaid Services (CMS) IDE Study Criteria

Medicare Beneficiaries

The results of this study are expected to be generalizable to the Medicare population based on the incidence of uncontrolled hypertension and estimates of the number of patients taking multiple antihypertensive medications.

Previous data from Symplicity HTN-3 showed that, on average, patients in both the renal denervation and sham procedure arms were on approximately 5 antihypertensive medications at baseline measurement. Approximately 28% of patients enrolled were age 65 or older.[35]

In addition, in a cross-sectional analysis of data from the Framingham Heart Study, only 48% of treated participants had their blood pressure controlled to <140/90 mm Hg. Among elderly participants (> 75 years of age), less than 40% had achieved a goal blood pressure. Framingham data also showed that older age was the strongest predictor of blood pressure being uncontrolled.[35]

L.7 Blood Pressure Measurement Procedures

1. OFFICE BLOOD PRESSURE

All Office Blood Pressure (OBP) Measurements must be taken with the automatic BP Monitor & printer (if applicable) as specified by the sponsor.

- At screening visit 1, the appropriate arm for study measures must be selected as specified in section A below and then used for all subsequent follow-up visits.
- For each study visit, the study visit should begin before 10:30am. This does not apply to Screening Visit 1 (if the subject is consented at SV1) and Unscheduled follow-up visits.

Patient should not take their antihypertensive medication in the morning of the visit, but rather bring the medication with them to the visit to have observed pill taking after office blood pressure measurement (if applicable). The requirement for not taking the medication in the morning of the visit does not apply to Screening Visit 1, if the subject signed the Informed Consent Form at SV1, medication reintroduction visit, unscheduled visits or at the discharge visit.

A. ARM SELECTION AT SCREENING VISIT 1 ONLY

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

B. PREPARATION AT ALL VISITS

(1) Ensure the BP monitor and all necessary equipment are functioning appropriately (per sponsor instructions).
(2) Confirm the subject did not drink coffee or alcohol, smoke, or exercise within 30 minutes prior to the measurements.
(3) Request the subject to use the bathroom prior to measurements (a full bladder can affect the reading).
(4) The subject should be seated comfortably with the back supported and 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 14 below) and that the upper arm is supported at the level of the heart (e.g. resting on a table at the level of his/her heart). The same cuff size should be used as selected at Screening Visit 1 for the remainder of the study.

Table 10: BP Cuff Size Chart

Cuff Size*	Fits Arm Circumference of (inches)	Fits Arm Circumference of (centimeters)
Small	7 – 9	17 – 22
Medium	9 – 13	22 – 32
Medium-Large	9 - 17	22 - 42
Large	13 – 17	32 – 42
Extra-Large**	17 – 20	42 – 50

* If a subject is on the border of two cuff sizes, opt for the larger of the two sizes

** Subjects requiring greater than an extra-large cuff size at time of screening must be excluded from the study

(6) Perform a "test" BP measure. Ensure test measurement is captured/recorded.

(7) Have the subject sit comfortably and quietly for at least 5 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)

C. METHOD FOR TAKING BP AT ALL VISITS

(1) General Instructions

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

b. Wait at least 1 minute between each measurement. **Ensure that the blood pressure monitor time clock is used for tracking the time intervals to avoid deviations due to insufficient wait time between measurements.**

c. Print (if available) and label after each measurement.

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

a. If the lowest and highest systolic BP (SBP) values of the first 3 consecutive measurements are >15 mmHg apart, take one additional reading and average the last 3 consecutive measurements (measurements 2-4). If the measurements are still >15 mmHg apart, take one additional reading and average the last 3 consecutive measurements (measurements 3-5). If the measurements are still >15 mmHg apart, take one final measurement and average the last 3 consecutive measurements (measurements 4-6).

(3) **At Screening Visit:** If the lowest and highest SBP values for the readings are more than 20 mmHg apart after 6 measurements, the subject must be excluded from the study.

(4) **At all Subsequent Follow Up Visits:** If the lowest and highest SBP values for the readings are more than 20 mmHg apart after 6 measurements, take the average of the last three measurements (measurements 4 – 6) and record the value on the CRF.

(5) Record the **last** 3 consecutive, consistent readings on the CRF (i.e. cannot pick the 'best' 3).

NOTE: *To better ensure long-term preservation of the OBP source data, a photocopy labeled as certified of all automatic BP Monitor printouts (if applicable) should be made and attached to the originals. If unable to print, document BP & HR values, dates and exact times of readings, and label appropriately.*

Orthostatic Hypotension Evaluation (AT SCREENING VISIT 2 ONLY)

In addition to the seated OBP recordings above, measure supine and standing BPs.

(1) Have the subject lie supine for at least 5 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.
   - Evaluate for any symptoms (e.g., dizziness) that may occur in the subject within the first 3 minutes after standing.

2. AMBULATORY BLOOD PRESSURE MONITORING

All 24 Hour Ambulatory Blood Pressure Monitoring (ABPM) measurements must be taken with the 24-hour ABPM device provided by the sponsor to ensure consistency.

Cuff size identified at SV2 should be used for the duration of the study.

(1) If the subject is on antihypertensive medications, the visit should begin before 10:30am unless the subject normally takes their antihypertensive medication in the afternoon in which the subject's visit can occur in the afternoon.

(2) Study personnel should observe the subject swallowing the antihypertensive medication(s), if applicable. Once this is completed and documented, the ABPM device should be applied to the subject and the recording started before leaving the office.

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

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

(5) The ABPM has pre-set parameters and should not be adjusted. These parameters are set to record blood pressure every 30 minutes.

(6) Instruct subjects that they should engage in their usual physical level but should avoid strenuous exercise during the monitoring period

(7) Instruct the subject to hold the arm still by the side while the device is taking a reading

(8) Upon the return of the ABPM machine:
   - Submit the 24 Hour ABPM data to Medtronic
   - 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. At SV2, a single repeat ABPM will be allowed in case of th following:
     - If the 24-hr systolic ABPM measured is between 135 and <140 mmHg or 170-175 mmHg
     - If a valid number of readings is not obtained
     - If there is a technical issue with the blood pressure monitor or failure to follow ABPM instructions.

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

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

L.8 Sample Patient Information and Informed Consent Form

Geography-specific informed consents will be provided separately.

L.9 Subject Blinding Assessment

Assessment will be provided separately.

L.10 EQ-5D (Quality of Life) Survey

Geography-specific EQ-5D will be provided separately.

L.11 SF-36 (Quality of Life) Survey

L.12 ABPM Guidelines

Guidelines will be provided separately.

L.13 Serious or Unanticipated Adverse Event Report (Rush form)- *Japan only*

Rush form only applies to Japan and will be provided separately.

L.14 Angiographic Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.

L.15 Renal Duplex Ultrasound (DUS) Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.

L.16 Magnetic Resonance Angiography (MRI)/Computerized Tomography (CT) Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.

L.17 Blood Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.

L.18 Drug Testing Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.