Medtronic

SPYRAL HTN-ON MED

Clinical Investigation Plan

Version 10.0

10 September 2020

IDE #: G150036

NCT#:

NCT02439775

Global Sponsor	
Medtronic Vascular, Inc. 3576 Unocal Place Santa Rosa, California 95403 United States Phone: +1 (800) 633-8766 Note: this clinical study is funded by the sponsor	
Regional Sponsors	
Medtronic Australasia Pty. Ltd 2 Alma Road, Macquarie Park, NSW 2113 Australia Phone: (+61) 2 0 9857 9000	Medtronic Bakken Research Center (BRC) B.V. Endepolsdomein 5, 6229 GW Maastricht, The Netherlands Phone: +31-43-35-66-566
Medtronic of Canada, Ltd. 99 Hereford Street Brampton, Ontario, L6Y 0R3 Canada Phone: +1-800-268-5346	Medtronic Japan Co., Ltd 1-2-70 Konan, Minato-ku, Tokyo 108-0075 Japan Phone: (+81) 3-6774-4611

Approval sheet

Author/Medical Writer/Clinical Study Manager (document owner):

Pamela McKenna	**Sr. Prin. Clinical Research Specialist**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)

Clinical Leadership:

Vanessa DeBruin	**Clinical Research Director**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)
Sandeep Brar	**Sr. Clinical Research Director**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)
Vinny Parthasarathy	**APAC CL Lead**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)
Christina Zhong	**VP of Clinical Research**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)
Garrett Pilcher	**Sr. Clinical Research Director**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)
Aarthi Kamath	**Sr. Clinical Research Specialist**

(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)

Statistics Management:

Minglei Liu	**Senior Statistics Manager**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)

QA:

Jennifer Loushin	**Senior Clinical Quality Compliance Specialist**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)

Regulatory Affairs:

Anna Dyer	**Regulatory Affairs Manager**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)

Safety:

Carine Van Deursen	**Clinical Safety Specialist**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)

Monitoring:

PJ Belmont	**Sr. Clinical Research Monitor**
(name)	(functional role)
Electronic sign-off	**Electronic sign-off**
(signature)	(date) (dd MMM yyyy)

Therapy Subject Matter Expert:

Oscar Sanchez	**Sr. Clinical Research Manager**
(name)	(functional role)

Electronic sign-off	Electronic sign-off
(signature)	(date) (dd MMM yyyy)

Change History record

CIP Change History		
Version	**Summary of Changes**	**Author**
1.0	*Initial*	Vanessa DeBruin
2.0	*Changes include the list below:* *1. Updated Time Course.* *2. Revisions of exclusion criteria.* *3. Updated/clarified safety and efficacy endpoints.* *4. Added baseline duplex ultrasound if obtained per standard of care.* *5. Updated anti-platelet/anti-coagulation language.* *6. Added Drug testing for Hypertensive Crises.* *7. Added/revised adverse event reporting language in Japan and Australia.* *8. Added contact information for the services providers.* *9. Updated Blood Pressure Measurement Procedures.* *10. Added list of Appendices.* *11. 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. Updated screening criteria.* *6. Clarified study ISO14155:2011 compliant except for AEs not reported for Control subjects after 12 months post-randomization.* *7. Updated Section E.6 Study device/product traceability.* *8. Updated Section F Study Methods.* *9. Revised Figure 8 for consistency with protocol changes.* *10. Added CT/MRA Service Provider on Section L.1.1.* *11. Updated Section L.7 Blood Pressure Measurement Procedures.* *12. Minor formatting, typo, and clarifying language changes throughout protocol.*	Vanessa DeBruin
4.0	*Changes include the list below:* *1. Updated total number of subjects to be randomized from 100 to 110.* *2. Removed "non-fasting" when referring to blood draws.* *3. Added "Updated address for Cardiovascular Research Foundation.* *4. Removed statement that a 6 French sheath should be used for renal angiogram.*	Vanessa DeBruin
5.0	*Changes include the list below:* *1. Updated approval signatories.* *2. Updated study purpose throughout protocol to include hypothesis test.*	Kelsey Anderson

	3. *Added reference to inclusion of additional geographies, including Canada and applicable regulatory requirements.* 4. *Updated/Clarified Safety and Efficacy Endpoints.* 5. *Updated Time Course.* 6. *Updated randomization ratio to 2:1.* 7. *Updated total number of subjects to be screened from 750 to 1600.* 8. *Updated total number of participating study centers from 25 to 55.* 9. *Added 6-month crossover option for sham control subjects.* 10. *Revisions of inclusion and exclusion criteria.* 11. *Updated Follow-up Schedule.* 12. *Updated interim analyses from 40, 60 and 80 subjects randomized to 175 and 220 randomized.* 13. *Updated Procedures section.* 14. *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.* 15. *Updated Clinical Experience section.* 16. *Updated G3 generator manufacturer, Plexus Corp. address.* 17. *Updated Sample Size section.* 18. *Updated Training Requirements section.* 19. *Added in 12M CTA/MRA Renal Imaging requirement for "a minimum of 50 and up to 340 patients" throughout the protocol.* 20. *Added requirement to repeat office blood pressure and drug testing upon ABPM repeat.* 21. *Updated Unavoidable Adverse Events Table.* 22. *Updated Adverse Event Reporting Requirements Table.* 23. *Clarified Investigator CRF signature requirements.* 24. *Updated screening criteria.* 25. *Revised Figures and Tables Throughout Protocol for Consistency with Protocol Changes.* 26. *Updated Data Analysis and Reporting section.* 27. *Minor formatting, typo, and clarifying language changes throughout protocol.*	
6.0	*Changes include the list below:* 1.) *Added 36 month follow-up visit for crossover subjects.* 2.) *Updated > the range of 60-70% to >60% to indicate that anything above the range of 60-70% identified by DUS will require repeat imaging.*	Marianne Wanten
7.0	*Changes include the list below:* 1. *Update to indicate that SV1 can occur after 10.30 am if Informed Consent Form is signed at SV1, without a protocol deviation.* 2. *Clarified that at least one antihypertensive medication needs to be at 50% of the maximum dose to qualify for the study.* 3. *Added that subjects cannot be on other antihypertensive medications.* 4. *Update to indicate no protocol deviation is required for not measuring hs-CRP when the site is unable to perform this blood test.*	Pamela McKenna

	5. *Added to exclusion criteria #9 that HbA1C will need to be re-analyzed if the value in the medical records is >3months old or if history of uncontrolled blood sugars raises concern.* 6. *Exclusion criteria #13: updated to state "individual with a history of narcotic drug abuse, is currently on Methadone, or who has used narcotic drugs more than once in the month prior to Screening Visit 1".* 7. *Exclusion criteria # 16: updated to indicate that subjects need to be off NSAIDs for 1 month prior to SV2, not enrollment.* 8. *Updated exclusion criteria # 18 to exclude Transient Ischemic attacks, or cerebrovascular accident altogether and not just if occurred within 3 months of screening. Added that patients who received catheter or surgical treatment for Atrial Fibrillation and are in sinus rhythm are not excluded.* 9. *Updated statistics section, including sample size section and interim analyses.* 10. *Updated Table 3 to include EQ-5D needed at 24/36M.* 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. *Update to clarify that patients who sign consent at SV1 are permitted to take their medication in the morning without protocol deviation.* 14. *Updates to reflect OBP device without printer* 15. *Minor formatting, typo and clarifying language changes throughout the protocol.*	
8.0	*Changes include the list below:* 1. *Updated Section F5 to include alternate Follow-up methods to allow more flexibility* during extenuating circumstances, such as a global pandemic. 2. *Sample size updated* 3. *Addition of clarification around when first and second interim analyses will take place.* 4. *Planned completion of randomization changed to January 2021 and planned study close-out changed to July 2024.* 5. *Update to escape criteria that subject must meet the escape criteria and have medication changes in response.* 6. *Update to analysis sets noting requirement of medication changes.* 7. *12-month imaging requirements clarified for UK and German subjects* 8. *Updated table 10.* 9. *Incorporated latest ISO1455 updates.* 10. *Formatting and administrative updates.*	Pamela McKenna
9.0	1. *Administrative update to remove the following sentence from the section F.5 '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 8.0 of the CIP which was not implemented prior to version 9.0.*	Pamela McKenna
10.0	1. *Updated sample size for first interim analysis.* 2. *Updated operating characteristics for primary efficacy endpoint.*	Pamela McKenna

Table of Contents

A SYNOPSIS 13

B GENERAL INFORMATION 22

B.1 Introduction 22

B.1.1 Clinical Experience Using the Single Electrode RF Renal Denervation System 22

B.1.2 Clinical Experience Using the Multi Electrode RF renal denervation system (Spyral) 25

B.2 Device information 31

B.2.1 The Symplicity™ renal denervation system 31

B.2.2 Symplicity Spyral™ Catheter 31

B.2.3 Symplicity G3™ Generator 32

B.2.4 Labeling 34

B.2.5 Intended clinical performance 34

B.3 Comparator information 35

C STUDY PLAN 36

C.1 Study Objective 36

C.2 Clinical endpoints 36

C.2.1 Primary Endpoints: 36

C.2.2 Secondary Endpoints 37

C.3 Study Population 39

C.4 Study Design 39

C.5 Randomization and blinding 39

C.6 Sample Size 40

C.7 Number of investigation sites and study duration 42

D SUBJECT SELECTION 42

D.1 Inclusion criteria 42

D.2 Exclusion criteria 42

E STUDY PREPARATION PROCEDURES 44

E.1 Investigator/Investigation site selection 44

E.1.1 Investigator selection criteria 44

E.1.2 Investigational site selection criteria 45

E.1.3 Clinical Trial Agreement 45

E.1.4 Curriculum Vitae 45

E.2 Ethics 46

E.2.1 EC/IRB approval 46

E.2.2 Patient Information and Informed consent process 46
E.2.3 Revisions in Patient Information and Informed Consent Form 47
E.2.4 Regulatory submission 47
E.3 Regulatory compliance 48
E.4 Training requirements 48
E.5 Clinical study materials and clinical study-specific equipment 49
E.6 Study device/product handling and traceability 49
E.6.1 Supply of investigational devices/products 50
E.6.2 Storage and handling of investigational devices/products 50
E.6.3 Device explant and return procedures/products 50
E.6.4 Device/product disposition requirements 51
F STUDY METHODS 51
F.1 Point of enrollment 51
F.2 Screening Visit 1 53
F.3 Screening Visit 2 53
F.4 Procedure 55
F.5 Follow-Up Procedures 57
F.6 Crossover Procedures 60
F.7 Confirmatory Blood Draws to Assess Renal Function 63
F.8 Antihypertensive medication escape criteria 63
F.9 Drug testing for Emergency Room Visit or Hospitalization for Elevated Blood Pressure 64
F.10 Data collection requirements 64
F.11 Role of the sponsor's representatives 67
F.12 Source documents 67
F.13 Adverse events and device deficiencies 67
F.13.1 Definition/classification 67
F.13.2 Recording, reporting, and review of Adverse Events 69
F.13.3 Recording, reporting, and review of Device Deficiencies 70
F.13.4 Adverse Event Reporting Requirements 71
F.13.5 Data Safety Monitoring Board and Clinical Events Committees 73
F.13.6 Emergency contact details in case of serious AEs 73
F.14 Subject accountability 73
F.14.1 Missed Follow-up Visits 73
F.14.2 Unscheduled Follow-up Visits 74
F.14.3 Subject Withdrawal or Lost to Follow-up 74
F.14.4 Subject Exit from Trial 74
F.15 Study deviations and CIP changes 75

F.15.1 Request for Approval of Study Deviations 75
F.15.2 Reporting requirements for study deviations 75
F.15.3 Amendments to the Clinical Investigation Plan 76
G QUALITY CONTROL PROCEDURES 77
G.1 Procedures for database management 77
G.1.1 Data collection 77
G.1.2 Source data to be directly recorded on the Case Report Forms 77
G.1.3 Time windows for completion and submission of Case Report Forms 77
G.1.4 Data review and processing 77
G.2 Monitoring procedures 77
G.2.1 Accessibility of investigational site staff and study materials 78
G.2.2 Audits and investigation site inspections 78
G.3 Study suspension or early termination 78
G.3.1 Early Study Suspension or Termination 79
G.3.2 Early investigation site suspension or termination 79
G.3.3 Subject follow-up in case of termination 79
G.3.4 Criteria for unblinding 80
G.4 Study close out 80
H DATA ANALYSIS AND REPORTING 80
H.1 Analysis of clinical data 81
H.2 Primary Safety Objective 82
H.3 Secondary Safety Objectives 83
H.3.1 Renal Artery Stenosis Evaluation at 12 Months 83
H.4 Primary Efficacy Objective 83
H.4.1 Primary Efficacy Endpoint Operating Characteristics 84
H.5 Secondary Efficacy Objectives 85
H.6 Additional Objectives 85
H.7 Safety Evaluation 86
H.8 Subgroup Analyses 86
H.9 Publication Policy 87
I STUDY MANAGEMENT 87
I.1 Study staff 87
I.2 Advisory committees 88
I.2.1 Executive Steering Committee 88
I.2.2 Data Safety Monitoring Board (DSMB) 88
I.2.3 Clinical Events Committee (CEC) 88
I.2.4 Publications Review Committee 89

I.3 Records and reports 89
I.3.1 Investigator records 89
I.3.2 Investigator reporting responsibilities 90
I.3.3 Sponsor records 91
I.3.4 Sponsor reporting responsibilities 91
I.3.5 Record retention 92
I.4 Miscellaneous 92
I.4.1 Insurance 92
I.4.2 Subject compensation and indemnification 92
I.4.3 Subject confidentiality 93
J RISKS AND BENEFITS 93
J.1 Anticipated Clinical Benefits 93
J.2 Risks 94
J.3 Minimization of Risk 96
J.4 Risk-to-Benefit Rationale 97
K REFERENCES 97
L APPENDICES 100
L.1 Names and addresses 100
L.1.1 List of contact persons 100
L.1.2 List of participating investigation sites and investigators 102
L.2 Case Report Forms 102
L.3 Sample Investigator Agreement 102
L.4 Abbreviations 103
L.5 Definitions 106
L.6 Center for Medicare and Medicaid Services (CMS) IDE Study Criteria 106
L.7 Blood Pressure Measurement Procedures 108
L.8 Sample Patient Information and Informed Consent Form 111
L.9 Subject Blinding Assessment 111
L.10 EQ-5D (Quality of Life) Survey 111
L.11 ABPM Guidelines 111
L.12 Serious or Unanticipated Adverse Event Report (Rush form) – *Japan only* 111
L.13 Angiographic Core Laboratory Guidelines 111
L.14 Renal Duplex Ultrasound (DUS) Core Laboratory Guidelines 111
L.15 Magnetic Resonance Angiographic (MRA) / Computerized Tomography (CT) Core Laboratory Guidelines 111
L.16 Blood Core Laboratory Guidelines 111
L.17 Drug Testing Core Laboratory Guidelines 111

A SYNOPSIS

Title

Global Clinical Study of Renal Denervation with the Symplicity Spyral™ multi-electrode renal denervation system in Patients with Uncontrolled Hypertension on Standard Medical Therapy.

Purpose

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

Design

Multi-center, international, prospective, blinded, 2:1 (treatment to control) 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 on one, two, or three standard antihypertensive medications compared to a sham-controlled population. 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 will be used to confirm the effect of renal denervation on elevated blood pressure in patients on 1, 2 or 3 antihypertensive medications. Data collected during the SPYRAL HTN-ON MED trial may be used to gain market approval or additional indications 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 Device Agency (PMDA), Health Canada, and the U.S. Food and Drug Administration (FDA).

Endpoints

Primary Endpoints

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

Powered Primary Efficacy Endpoint:

- Baseline adjusted change (using Analysis of Covariance) in systolic blood pressure (SBP) from baseline (Screening Visit 2) to 6 months post-procedure as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM).

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 and/or the protocol.
    - New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core laboratory

Secondary Endpoints

Secondary Efficacy Endpoints

- 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
- 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
- Change in office diastolic 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

Secondary Safety Endpoints

- Acute/procedural safety 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
    - Increase in serum creatinine >50% from Screening Visit 2
    - 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)
- 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 medication and/or protocol

- Chronic Safety Secondary Endpoints at 3, 6, 12, 24 and 36 months post-procedure
  - Composite Safety Endpoint, defined as a composite of the following events:
    - All-cause mortality
    - End-Stage Renal Disease (ESRD)
    - Significant embolic event resulting in end-organ damage
    - Renal artery perforation requiring intervention
    - Renal artery dissection requiring intervention
    - Vascular complications
    - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications and/or the protocol.
    - New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core laboratory
  - ≥ 40% decline in eGFR
  - Increase in serum creatinine >50% from Screening Visit 2
  - New Myocardial Infarct
  - 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)
  - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medication and/or protocol
- Summary of Health-related Quality of Life (HRQoL) analysis based on reporting measures using accepted QoL instruments (EQ5D)

Additional analyses

The following additional analyses will be conducted:

- Antihypertensive medication usage throughout the study, including escape patients and subjects with medication changes within 6-month follow-up.
- 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.
- Medication adherence using results from drug testing. In addition, we will perform analyses to evaluate the effect of medications adherence on BP.
- Long term imaging of renal arteries

Subject population

Patients with uncontrolled hypertension on one, two, or three antihypertensive medications (of which at least one is at least 50% of maximum manufacturer's recommended dosage of a thiazide-type diuretic, a dihydropyridine calcium channel blocker, an ACE-inhibitor/angiotensin receptor blocker (ACE-I/ARB), or a beta blocker) will be enrolled in accordance with the Inclusion and Exclusion criteria specified in the protocol. Subjects cannot be on other antihypertensive medications. Note: In Japan, patients may be prescribed less than 50% of maximum manufacturer's recommended dosage of a thiazide-type diuretic per standard of care. Approximately 1600 subjects will be screened in order to randomize approximately 340 subjects (including up to 80 subjects used as an informative prior see Section C.6), at up to 55 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 in the prospective cohort is expected to take approximately 20 months.

Subjects are expected to participate in the study from the time of signing consent until completion of three to six years of follow-up after randomization as described in Table 1 and Table 2. If a subject is randomized to the renal-denervation arm their participation will be 3 years. If a subject is randomized to the control (sham) arm, they may be offered renal denervation therapy (crossover) after their 6-month follow-up visit and will, if they undergo crossover denervation therapy, continue to be followed for 36-months after the renal-denervation procedure, according to Table 2. There will be some subjects that receive the crossover visit after their 6-month visit, for those subjects the participation time will be increased to a maximum of 6 years, specifically for any subject that is offered the crossover procedure at the 36-month follow visit as they will need to be followed for 36-months following the crossover.

Screening Criteria

Eligible patients will be screened for participation into the study if they are aged 20-80 years, have a diagnosis of hypertension, are taking one, two, or three antihypertensive medications of which at least one is at least 50% of maximum manufacturer's recommended dosage of a thiazide-type diuretic, a dihydropyridine calcium channel blocker, an ACE-I/ARB or a beta blocker (When prescribed with other qualifying medications, 12.5 mg hydrochlorothiazide is acceptable as the minimum dosage) for at least six weeks prior to screening visit 1 and who 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). Note: In Japan, patients may be prescribed less than 50% of maximum manufacturer's recommended dosage of a thiazide-type diuretic per standard of care. If a patient is initially screened per inclusion criterion 2 on a certain number of medications (e.g., two) and screen fails with an OBP > 140 mmHg but < 150 mmHg, the subject may subsequently be re-screened at least 6 weeks after the medication change for the study as long as the patient is on fewer medications (but still meeting minimum medication requirements) than when initially screened.

Inclusion Criteria

1. Individual is ≥ 20 and ≤ 80 years old at time of enrollment (consent).
2. Individual has an office systolic blood pressure (SBP) ≥ 150 mmHg and < 180 mmHg and an office diastolic blood pressure (DBP) ≥ 90 mmHg (according to guidelines in Appendix L.7) at Screening Visit 1 and Screening Visit 2 when receiving a medication regimen of one, two, or three antihypertensive medication classes of which at least one is at least 50% of the maximum manufacturer's dosage. The antihypertensive medication classes must include a thiazide-type diuretic, a dihydropyridine calcium channel blocker, an ACE-I/ARB, or a beta blocker and the subject must be on a stable dose of each medication for at least six weeks prior to Screening Visit 1 and up to Screening Visit 2. When prescribed with other qualifying medications, 12.5 mg hydrochlorothiazide is acceptable as the minimum dosage. Note: In Japan, patients may be prescribed less than 50% of maximum manufacturer's recommended dosage of a thiazide-type diuretic per standard of care.

3. Individual has a valid 24-hour ABPM average of SBP ≥ 140 and < 170 mmHg measured at Screening Visit 2 according to guidelines in Appendix L.7 after witnessed antihypertensive drug ingestion prior to applying the ABPM device. (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.

Exclusion Criteria

1. Individual has undergone prior renal denervation.
2. Individual has renal artery anatomy that is ineligible for treatment including:
    a. Main renal artery for each kidney is less than 3mm or greater than 8mm
    b. Lacks a main renal arterial vessel 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 between 3mm and 8mm)
3. Presence of FMD (fibromuscular dysplasia) (defined as visible beading of the artery on angiography)
4. Has >50% stenosis in any treatable vessel.
5. Has a renal artery stent placed <3 months prior to the denervation procedure.
6. Presence of an aneurysm defined as any localized increase in the diameter of the vessel
7. 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
8. 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).
9. Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%. (If the glycosylated hemoglobin in the patient's records is >3 months old (from the date of SV2), or history of uncontrolled blood sugars raises concern it is required to analyze glycosylated hemoglobin as part of SV2 labs.)
10. 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.
11. 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).
12. Individual requires chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea (e.g. CPAP, BiPAP).
13. Individual with a history of narcotic drug abuse, is currently on Methadone, or who has used narcotic drugs more than once in the month prior to Screening Visit 1.
14. Individual has documented primary pulmonary hypertension.
15. Individual has untreated secondary cause of hypertension (either known or suspected) or is taking drugs that increase sympathetic tone that could contribute to hypertension.
16. 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. (Patients are permitted to take aspirin or clopidogrel for cardiovascular risk reduction).

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

Treatment

Subjects taking one, two, or three eligible antihypertensive medications for at least six weeks and with an office SBP ≥ 150 mmHg and < 180 mmHg and an office DBP ≥ 90 mmHg can be enrolled and proceed to Screening Visit 1 (SV1). Subjects meeting the eligibility criteria can continue to Screening Visit 2 (SV2) 2-4 weeks after SV1. Subjects who continue to meet eligibility criteria after completion of SV2 and who have received randomization approval by the sponsor will be randomized and the

procedure will occur within a maximum of two weeks (14 calendar days) following the completion of SV2. Subjects must not meet any anatomic exclusion criteria in aortography or renal angiography to continue in the study.

Following the renal denervation or control procedure, subjects will complete follow-up at 1, 3, 6, and 12 months. Subjects and blinded study personnel will be unblinded to their randomization assignment upon completion of the 6-month follow-up. All subjects will be followed annually through 36 months post-procedure (Table 1). Control (sham) subjects may be offered renal denervation therapy (crossover) after the completion of their 6-month follow up visit and ensuring they meet key inclusion criteria and no key exclusion criteria. If a subject undergoes the crossover denervation therapy, they will be followed for 36 months after the renal-denervation procedure, according to Table 2 and Section F.6. For subjects who undergo crossover at a later time, they will be followed for 36 months from when the crossover occurred.

Interim Analyses

Interim analyses will take place after a minimum of 110 and 149 subjects (excluding the first consecutively randomized 80 subjects in the SPYRAL HTN-ON MED Study) have 6-month efficacy endpoint data available. This will require randomizing approximately 130 and 175 subjects to account for attrition. A decision to stop or continue the study will be made after each interim analysis has been reviewed.

Time Course

Start of enrollment (consent): July 2015

Planned completion of randomization: January 2021

Planned study close-out: July 2024

Clinical Procedures

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

1 month (30 days): 16-44 days, 3 months (90 days): 76-104 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 (M=months ± 14 days for 1M, 3M and 6M visits, ± 30 days for 12M-36M visits)**						
Required Assessments	**SV1**	**SV2**	**Procedure**	**Prior to Discharge**	**1M**	**3M**	**6M**	**12M**	**24M**	**36M**
Medical History	X									
Clinical assessment		X			X	X	X	X	X	X
Renal Denervation or Sham Procedure			X							
Office Blood Pressure according to guidelines in Appendix L.7	X	X		X	X	X	X	X	X	X
24-Hour ABPM according to guidelines in Appendix L.7		X				X	X	X	X	X
Witnessed pill taking		X				X	X	X	X	X
Blood tests (uric acid, lipid panel and high sensitivity CRP[6])		X								
Blood Tests (Chem-7)[3]		X		X	X	X	X	X	X	X
Serum or Urine Pregnancy Test		X								
Drug testing		X				X	X	X	X	X
Renal Artery Imaging – Angiogram			X							
Renal Artery Imaging		X[4]					X[1]	X[5]	(X)[5]	(X)[5]
Blinding Assessment for Subjects and Assessors				X		X	X			
EQ-5D		X				X	X	X	X	X
Mortality Assessment[2]					X	X	X	X	X	X
Medication Review and Event Review	All adverse events (AE) and all medication review After 12 months, previously reported AEs will need to be reviewed and updated as needed								Serious AEs and all medication review	

[1] DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CTA 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 if crossover is completed within 30 days of 6M visit.

[2] Conduct if follow-up missed.

[3] Bicarbonate will not be measured for subjects enrolled in Japan and Europe.

[4] Submit baseline duplex ultrasound, CT, or MRA if obtained per standard of care prior to procedure within one year from the date of screening visit 1.[5] CTA/MRA required as first line imaging modality at 12M (and 24M and 36M as applicable). For treatment and crossover subjects only: 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 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.[6] 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 (30 days): 16-44 days, 3 months (90 days): 76-104 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 (M=months ± 14 days for 1M, 3M and 6M visit, ± 30 days for 12M-36M visits)				
Required Assessments	**Baseline[5]**	**Renal Denervation**	**Prior to Discharge**	**1M**	**3M**	**6M**	**12M**	**24M**	**36M**
Clinical assessment	X			X	X	X	X	X	X
Blood Tests (Chem-7)[3]	X		X	X	X	X	X	X	X
Blood Tests (uric acid, lipid panel, and high-sensitivity CRP[6])		X (prior to procedure)[5]							
Office Blood Pressure according to guidelines in Appendix L.7	X		X	X	X	X	X	X	X
Serum or Urine Pregnancy Test		X (prior to procedure)[5]							
Witnessed pill taking	X				X	X	X	X	X
24-Hour ABPM according to guidelines in Appendix L.7	X				X	X	X	X	X
EQ-5D	X				X	X	X	X	X
Renal Denervation		X							
Renal Artery Imaging - Angiogram		X							
Renal Artery Imaging						X[1]	X[4]	(X)[4]	(X)[4]
Drug Testing	X				X	X	X	X	X
Mortality Assessment[2]				X	X	X	X	X	X
Medication Review, Event Review	All adverse events (AE) and all medication review After 12 months, previously reported AEs will need to be reviewed and updated as needed							Serious AEs and all medication review	

[1] DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CTA 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.

[2] Conduct if follow-up visit missed.

[3] Bicarbonate will not be measured for subjects enrolled in Japan and Europe.

[4] 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 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.

[5] If not already collected at previous follow up visits (within 30 days of crossover procedure).[6] High-sensitivity CRP is not required to be measured for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed.

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 four 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 mmHg.

Ambulatory blood pressure recordings were available for 20 patients in the renal denervation group, showing a mean decrease of -11/-7 mmHg (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 mmHg [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 BP 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 crossover groups had significant and sustained blood pressure reductions.

Thirty-six months 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 mmHg 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 reduction in blood pressure 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 545 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 months 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 to 6.89, p=0.26], with a SBP reduction of 14.1 mm Hg 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 months 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 mm Hg 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-1, HTN-2 and HTN-3 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 for up to 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 crossover from sham to treatment after the completion of the 6-months follow-up visit. In the overview below, the office blood pressure results from all treated subjects with the data available at the time of study closure is shown in Figure 1.

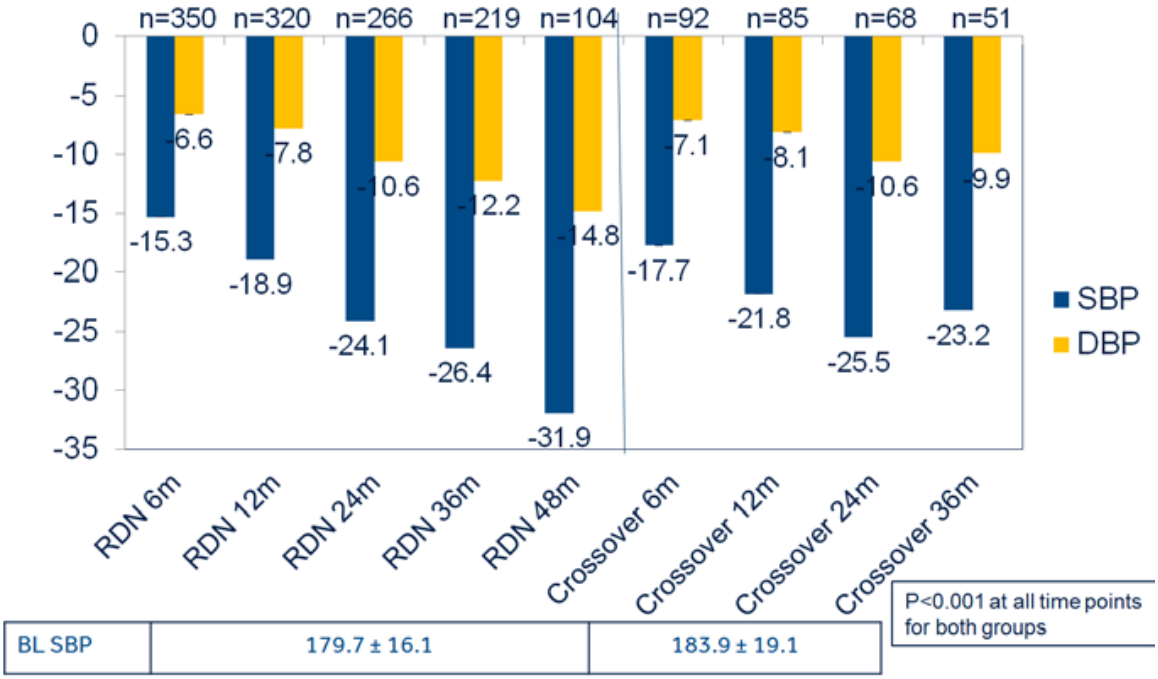

Figure 1: Change in Office Blood Pressure Through 36 and 48 Months Post-RDN

GLOBAL SYMPLICITY REGISTRY

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 15 May 2018, 2583 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 2583 subjects enrolled at the time of presentation at EuroPCR 2018, 2232 patients were treated with the Symplicity Flex™ catheter (Medtronic's first generation RDN catheter and 351 with the Symplicity Spyral™ catheter. 1035 subjects that were treated with the Symplicity Flex™ have 36-month follow-up data available, office blood pressure decreased on average by -16.47/-6.13 mmHg ($p<0.001$) from baseline to 36 months. In addition, 439 of those subjects had matched baseline and 6 months ABPM available at 36 months, although ABPM is not required in the GSR. In these subjects, the ambulatory systolic blood pressure reduction was -8.4 mmHg at 36 months.

In the 58 Spyral subjects with 36-month follow-up data available, office blood pressure decreased on average by -15.98 /7.14 mmHg ($p<0.001$) from baseline to 36 months. In addition, 26 subjects had ABPM data available at 36 months, although ABPM is not required in the GSR. In these subjects, the ABPM reduction was 17.62/6.19 mmHg ($p<0.05$) 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 at four centers were treated in Australia and New Zealand. Follow-up data through six months was presented at EuroPCR 2014[14]. 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 ABPM 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 ABPM 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 months 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 mmHg while 53.7% (22/41) had a systolic BP reduction of ≥ 20 mm Hg.

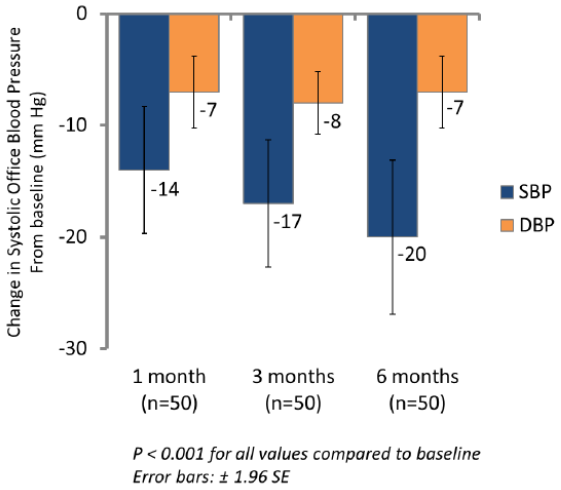

Figure 2: Change in Office Blood Pressure from Baseline through 6 Months

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 within 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 crisis and no end stage renal disease at the time of the 36 months 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 351 subjects in the Spyral sub-study was presented at EuroPCR 2018 with data out to two years for 175 subjects. Subjects presented with a mean ambulatory systolic blood pressure of 158 ± 18 Hg and a mean baseline office systolic blood pressure of 170 ± 18 mmHg. Ambulatory SBP showed sustained reductions to two years with a mean decrease of 13 mmHg. Sustained reductions in office SBP were also reported to two years with a mean reduction of 11 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 mmHg or greater and less than 180 mmHg, office diastolic blood pressure (DBP) of 90 mmHg or greater, and a mean 24-h ambulatory SBP of 140 mmHg or greater and less than 170 mmHg 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[13].

The primary endpoint, change in 24-hour blood pressure at 3 months, was compared between randomization 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.

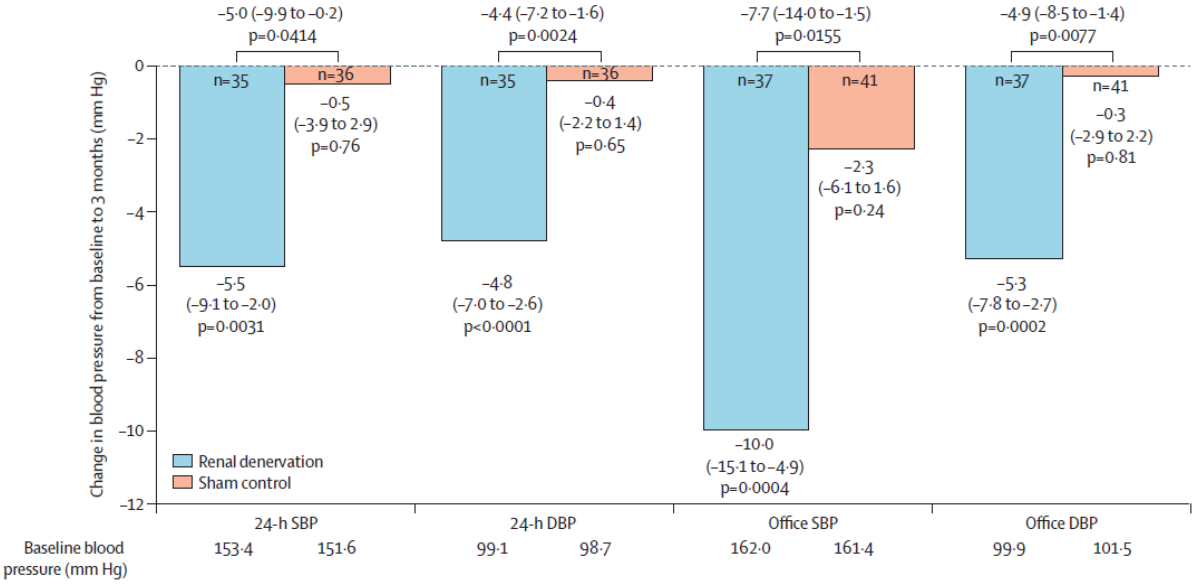

Figure 3: Changes at 3 Months iIn Office and Ambulatory SBP and DBP For Renal Denervation and Sham Control Groups

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).

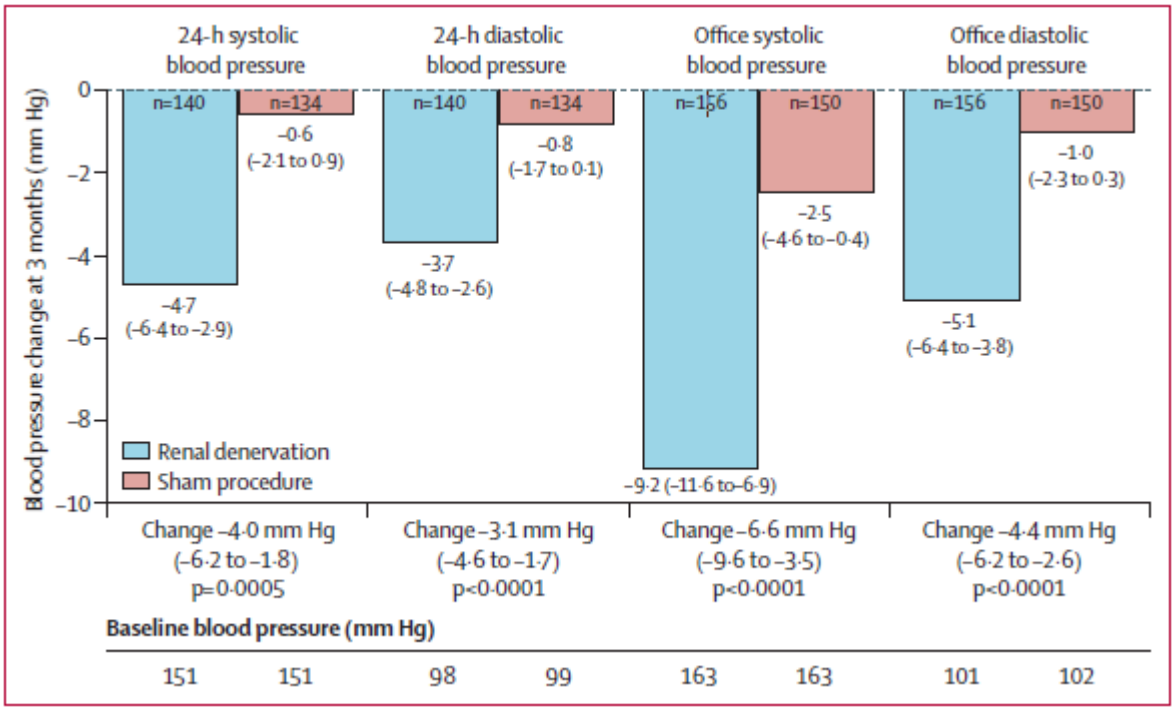

Figure 4: Changes in 24-h and office systolic and diastolic blood pressure from baseline to 3 months

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 Lancet[42]. 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.

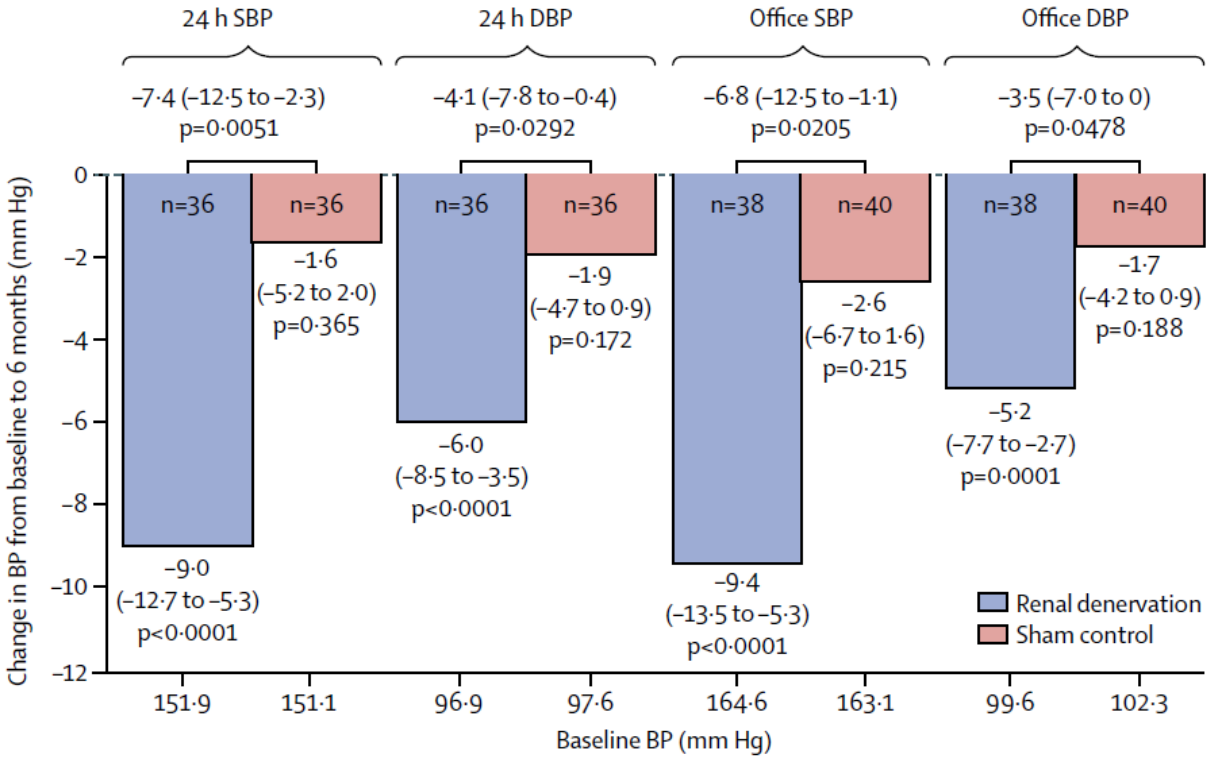

Figure 5: Changes at 6 Months in Office and Ambulatory SBP and DBP for Renal Denervation and Sham Control Groups

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 trial (36 months), the SYMPLICITY HTN-2 trial (36 months), as well as the data from the SYMPLICITY HTN-3 Trial (36 months) and the Global SYMPLICITY Registry.

The combined experience from these trials in over 4200 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 trials, 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 SPYRAL FIM, GSR Spyral sub-study, SPYRAL HTN-OFF MED Feasibility and SPYRAL HTN-ON MED Feasibility studies include over 420 patients and demonstrate safety and efficacy of the Spyral renal denervation system in resistant hypertensive, real-world, and off-medication populations. Specifically, results from the SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED trials provide

biological and real-world proof of principle for the efficacy of catheter-based renal denervation to reduce blood pressure in patients with hypertension not treated with antihypertensive medications and those on up to three antihypertensive medications, respectively. The SPYRAL HTN-OFF MED 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. This reduction was not observed in the sham control group. The SPYRAL HTN-ON MED study demonstrated a clinically significant reduction in office and 24-h ambulatory SBP and DBP at 6 months in patients with mild to moderate hypertension following renal denervation in the presence up to three antihypertensive medications. This reduction was not observed in the sham control group. There were no major safety events in either randomization group for either study. The aims of this study, SPYRAL HTN ON-MED, is to demonstrate that renal denervation, using Medtronic's next generation Symplicity Spyral™ catheter, decreases blood pressure and is safe when studied in the presence of up to three standard antihypertensive medications.

B.2 Device information

B.2.1 The Symplicity™ 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 gold 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.

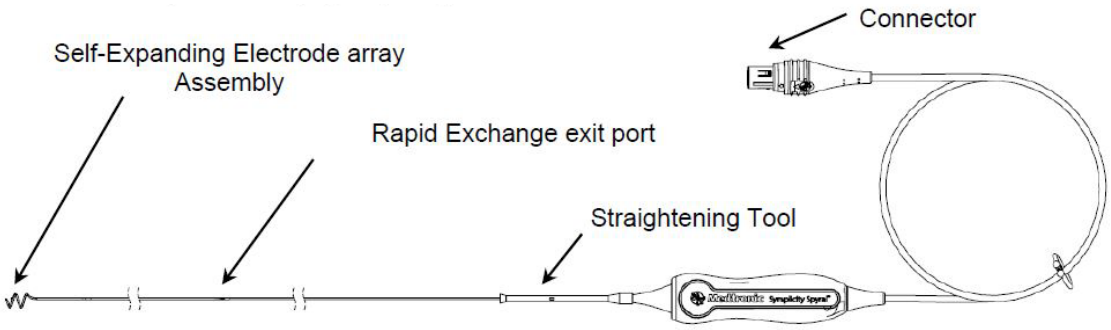

Figure 7: Overview of Symplicity Spyral™ Catheter

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 (Figure 8) 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™ catheter for controlled ablation of tissue. The Symplicity G3™ generator has been designed with the following features:

- Automated safety algorithms similar in all aspects of safety and energy delivery and stoppage to 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 Symplicity 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).

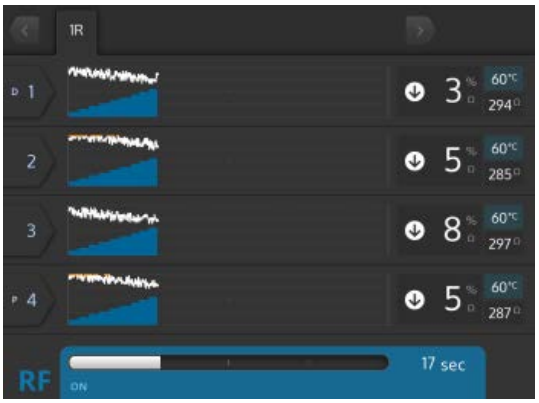

Figure 9: RF on Screen

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:

1. That the device is intended for investigational use in geographies where the product is not approved
2. Identification number
3. Model number
4. Lot/Serial number
5. Storage condition
6. Expiration date
7. 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 Figure 10) without adversely affecting the wall of the artery or surrounding organs.

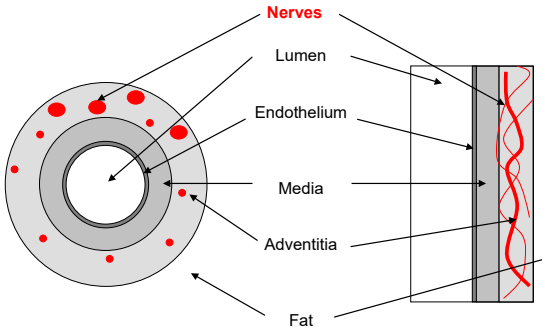

Figure 10: Illustration of renal artery anatomy

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, and hypothesis that this will result 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.

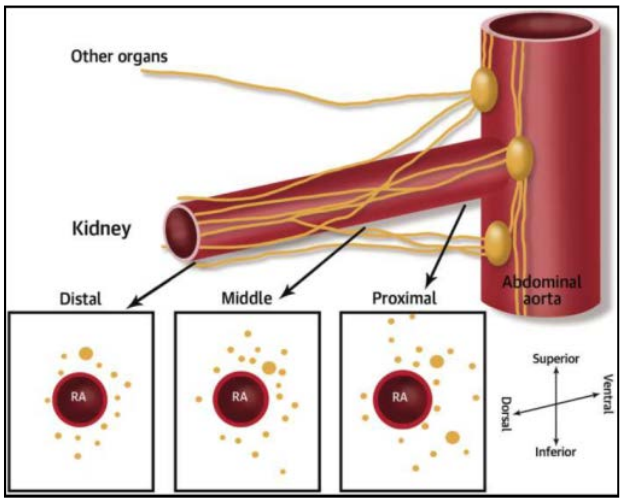

Figure 11: Illustration of peri-arterial renal nerve location

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 the SPYRAL HTN-ON 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 will study patients on up to three antihypertensive medications from three commonly used antihypertensive drug classes (i.e., the

standard medical therapy comparator).The approach used in SYMPLICITY HTN-3 where patients were required to be treated with ≥ 3 medications at maximum tolerated doses believed to have introduced variation and bias due to medication adherence issues and to significant medication changes throughout the course of the study as many patients had difficulties sustaining this type of drug regimen. For these reasons, where patients will be taking medications, the intent will be to keep them on their prescribed stable medication regimen throughout the SPYRAL HTN-ON MED study.

In this ON-MED study, a population with less severe hypertension, on fewer medications, and on medication not at maximum dose will be studied compared to the study population in SYMPLICITY HTN-3. This is consistent with the well-established pharmaceutical approach to drug approval where experience has showed it is possible to conduct a well-controlled study. Inclusion of a sham procedure will help "blind" the subject to their randomization group and ensure no other unmeasured factors are contributing to a change in blood pressure. Additionally, maintaining standard medication therapy will minimize changes in patient medications and potentially minimize the Hawthorne effect that is believed to have affected the efficacy outcomes in SYMPLICITY HTN-3.

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 presence of one, two, or three antihypertensive medications. In this study, "uncontrolled hypertension" means 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 in this study will help determine whether commonly used antihypertensive medications synergize, antagonize, or have no impact on the effect of renal denervation on blood pressure.

The data collected in the SPYRAL HTN-ON MED study may be used to gain market approval or additional indications for the Symplicity Spyral™ multi-electrode renal denervation catheter and the Symplicity G3™ renal denervation RF generator, from regulatory entities, including, but not limited to: the Pharmaceuticals Medical Device Agency (PMDA), Health Canada, and the U.S. Food and Drug Administration (FDA).

C.2 Clinical endpoints

C.2.1 Primary Endpoints:

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

Powered Primary Efficacy Endpoint:

- Baseline adjusted change (using Analysis of Covariance) in systolic blood pressure (SBP) from baseline (Screening Visit 2) to 6 months post-procedure as measured by 24-hour Ambulatory Blood Pressure Monitoring (ABPM).

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 and/or the protocol.
- New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core laboratory

C.2.2 Secondary Endpoints

Secondary Efficacy Endpoints

- 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
- 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
- Change in office diastolic 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.

Secondary Safety Endpoints

- Acute/procedural safety 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
  - Increase in serum creatinine >50% from Screening Visit 2
  - New Myocardial Infarct
  - 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)

- 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 medication and/or protocol

- Chronic Safety Secondary Endpoints at 3, 6, 12, 24 and 36 months post-procedure
  - Composite Safety Endpoint, defined as a composite of the following events:
    - All-cause mortality
    - End-Stage Renal Disease (ESRD)
    - Significant embolic event resulting in end-organ damage
    - Renal artery perforation requiring intervention
    - Renal artery dissection requiring intervention
    - Vascular complications
    - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications and/or the protocol.
    - New renal artery stenosis > 70%, confirmed by angiography and as determined by the angiographic core laboratory
  - ≥ 40% decline in eGFR
  - Increase in serum creatinine >50% from Screening Visit 2
  - New Myocardial Infarct
  - 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)
  - Hospitalization for hypertensive crisis not related to confirmed non-adherence with medication and/or protocol
- Summary of Health-related Quality of Life (HRQoL) analysis based on reporting measures using accepted QoL instruments (EQ5D)

Additional analyses

The following additional analyses will be conducted:

- Antihypertensive medication usage throughout the study, including escape patients and subjects with medication changes within 6-month follow-up.
- 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.
- Medication adherence will be assessed using results from drug testing. In addition, we will perform analyses to evaluate the effect of medications adherence on BP.
- Analyses looking at long term imaging will be performed.

C.3 Study Population

This study will randomize subjects who meet the criteria as detailed in the Subject Selection portion (Section D) of this Clinical Investigation Plan. Potentially eligible subjects will be consented and entered into a screening period to establish treatment eligibility. Approximately 340 subjects (including the first consecutively randomized 80 subjects in the SPYRAL HTN-ON MED Study) will be allowed to be randomized.

Eligible subjects will be randomized using a 2:1 (treatment to control) 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 HTN-ON MED study is a multi-center, international, prospective, blinded, randomized, interventional, sham-controlled study. The purpose of this study is to test the hypothesis that renal denervation decreases blood pressure and is safe when studied in the presence of one, two, or three anti-hypertensive medication classes. Subjects must be on at least one of these antihypertensive medications on at least 50% of the maximum manufacturer's dosage of antihypertensive medication. Antihypertensive medication classes must include a thiazide-type diuretic, a dihydropyridine calcium channel blocker, an ACE-I/ARB, or a beta blocker, (when prescribed with other qualifying medications, 12.5 mg hydrochlorothiazide is acceptable as the minimum dosage). Subjects cannot be on other antihypertensive medications. Study subjects will be randomized to the Denervation or Control group in a 2:1 (treatment to control) ratio. 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 6 months post procedure to prevent potential bias of results. See section C.5 for blinding techniques.

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 group subjects eligible for crossover.

It is anticipated that several subjects will no longer meet study eligibility after renal imaging, and measurement of OBP, ABPM, and renal function. Approximately 1600 subjects will be enrolled to randomize approximately 340 subjects (including the first 80 consecutively randomized in the SPYRAL HTN-ON MED study) in the study.

C.5 Randomization and blinding

Randomization will be stratified by study center at a 2:1 (treatment to control) 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 following the angiography. 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. To 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 effectiveness of blinding 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 with 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, the site personnel should 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 prior data. The discount function reduces the strength of the prior data if disagreements are observed with the prospective (subjects 81+) data.

The prior data consists of the first consecutively randomized 80 subjects in the SPYRAL HTN-ON MED Study which were randomized in a 1:1 ratio to RDN to sham control. The results from these 80 subjects have already been analyzed and published.

The prospective data consists of the following two cohorts:

1. Subjects 81 to 106 which have already been enrolled and were randomized in a 1:1 ratio to RDN vs sham control, and whose data has not been unblinded and analyzed by Medtronic.

2. All remaining subjects in the SPYRAL HTN-ON MED Study from 107 onwards which will be randomized in a 2:1 ratio to RDN vs sham control.

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 prospective data. The 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 prospective 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 prospective data compared to the prior, the prior will be weighted at or near 100%. If the prospective 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 110 to 221 evaluable subjects (not including the first consecutively randomized 80 subjects) due to the adaptive nature of the trial. This will require randomizing approximately 130 to 260 subjects to account for an expected 15% attrition at 6 months. The interim analyses will take place when a minimum of N=110 and N=149 subjects have 6-month follow-up data, with a maximum study size of 221 subjects if the study does not stop at either interim look.

The SPYRAL HTN-ON MED study will thus, randomize approximately up to 340 subjects. Interim analyses will be conducted and reviewed by the DSMB, along with an independent organization that will be performing the Bayesian analyses. At each interim analysis, enrollment may be stopped for futility or efficacy.

1. The first interim analysis takes place when a minimum of 110 subjects have evaluable 6-month efficacy data, requiring approximately 130 randomized subjects to account for 15% attrition. If the attrition rate is higher than 15%, then additional subjects will be randomized in order to reach a minimum of 110 evaluable. The Bayesian efficacy analysis will be performed and P[suc] will be calculated, where P[suc] represents the efficacy endpoint hypotheses, $P\left(\mu < 0 \middle| y, y_0, \widehat{\alpha_0}(y, y_0, \lambda, k)\right)$, and is defined in detail in section H4.
    a. If P[suc] > 0.975 then the study has met the efficacy hypothesis 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. The probability of futility is calculated based on the maximum study size of 221 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 the primary efficacy endpoint, then the study will have met the futility boundary and enrollment will be stopped. Further details can be found in the 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 then subject enrollment will continue to 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 the first 149 subjects have evaluable 6-month efficacy data, requiring 175 randomized subjects to account for attrition. If the attrition rate is higher than 15%, then additional subjects will be randomized in order to reach a minimum of 149 evaluable. The Bayesian efficacy analysis will be performed and P[suc] will be calculated.
    a. If P[suc] > 0.975 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. The probability of futility is calculated based on the maximum study size of 221 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 the primary efficacy endpoint, then the study will have met the futility boundary and enrollment will be stopped. Further details can be found in the 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 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 221 subjects with 6-month follow-up data (requiring

approximately 260 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 the primary efficacy hypothesis is met.

C.7 Number of investigation sites and study duration

This study is expected to be conducted in up to 55 study centers 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 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 in the prospective cohort is expected to take approximately 20 months. To minimize bias, individual investigational sites may randomize up to 20% of the total study subjects. 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 three years post-denervation procedure, if they (and their study doctor) agree to have the renal denervation procedure (crossover) after their 6-month follow-up.

If a site does not enroll any subjects 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 an office diastolic blood pressure (DBP) ≥ 90 mmHg (according to guidelines in Appendix L.7) at Screening Visit 1 and Screening Visit 2 when receiving a medication regimen of one, two, or three antihypertensive medication classes of which at least one is at least 50% of the maximum manufacturer's dosage. The antihypertensive medication classes must include a thiazide-type diuretic, a dihydropyridine calcium channel blocker, an ACE-I/ARB, or a beta blocker and the subject must be on a stable dose of each medication for at least six weeks prior to Screening Visit 1 and up to Screening Visit 2. When prescribed with other qualifying medications, 12.5 mg hydrochlorothiazide is acceptable as the minimum dosage. Note: In Japan, patients may be prescribed less than 50% of maximum manufacturer's recommended dosage of a thiazide-type diuretic per standard of care.
3. Individual has a valid 24-hour ABPM average of SBP ≥140 and < 170 mm Hg measured at Screening Visit 2, according to guidelines in Appendix L.7 after witnessed antihypertensive drug ingestion prior to applying the ABPM device. (ABPM is considered valid if the number of successful daytime readings captured is ≥ 21 and the number of successful nighttime readings captured ≥12).
4. Individual agrees to have all study procedures performed, and is competent and willing to provide written, informed consent to participate in this clinical study.

D.2 Exclusion criteria

1. Individual has undergone prior renal denervation.

2. Individual has renal artery anatomy that is ineligible for treatment including:
    a. Main renal artery for each kidney is less than 3mm or greater than 8mm
    b. Lacks a main renal arterial vessel 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 between 3mm and 8mm).
3. Presence of FMD (fibromuscular dysplasia) (defined as visible beading of the artery on angiography).
4. Has >50% stenosis in any treatable vessel.
5. Has a renal artery stent placed <3 months prior to the denervation procedure.
6. Presence of an aneurysm defined as any localized increase in the diameter of the vessel.
7. Treatment within 5mm of a segment in the renal artery which contains any of the following:
    a. Atheroma,
    b. Calcification, or
    c. Renal artery stent
8. 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).
9. Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%. (If the glycosylated hemoglobin in the patient's records is >3 months old (from the date of SV2), or history of uncontrolled blood sugars raises concern, it is required to analyze glycosylated hemoglobin as part of SV2 labs.)
10. 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.
11. 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).
12. Individual requires chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea (e.g. CPAP, BiPAP).
13. Individual with a history of narcotic drug abuse, is currently on Methadone, or who has used narcotic drugs more than once in the month prior to Screening Visit 1.
14. Individual has documented primary pulmonary hypertension.
15. Individual has untreated secondary cause of hypertension (either known or suspected) or is taking drugs that increase sympathetic tone that could contribute to hypertension.
16. 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 (patients are permitted to take aspirin or clopidogrel for cardiovascular risk reduction).
17. Individual with HIV on anti-retroviral drug therapy without documentation that hypertension preceded initiation of anti-retroviral drug treatment.
18. 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.

19. Individual has a scheduled or planned surgery that, in the opinion of the Investigator, may affect study endpoints.
20. Individual has a documented condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the protocol-specified automatic/office blood pressure monitor (e.g., upper arm circumference outside cuff size ranges available by geography or arrhythmia such as atrial fibrillation that interferes with automatic monitor's pulse sensing and prohibits an accurate measurement).
21. Individual works night shifts.
22. Individual has severe cardiac valve stenosis for which, in the opinion of the investigator, a significant reduction of blood pressure is contraindicated.
23. Individual has a documented confounding medical condition, which in the opinion of the investigator, may adversely affect the safety of the participant (e.g. patients with clinically significant peripheral vascular disease, aortic aneurysm, bleeding disorders such as thrombocytopenia, hemophilia, or significant anemia).
24. Individual is pregnant, nursing or planning to become pregnant during the course of the study follow-up. (Note: Pre-menopausal female participants must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test prior to angiography).
25. Individual has a known unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable, in the opinion of the investigator, to comply with study follow-up requirements.
26. Individual is currently enrolled in a concurrent investigational drug or device study, unless approved by the study sponsor. (Note: For the purpose of this protocol, participants involved in extended follow-up studies for products that were investigational but are currently commercially available are not considered enrolled in an investigational study).
27. Individual is currently taking anti-mineralocorticoid drugs. (Note: Subjects may be enrolled as long as anti-mineralocorticoid drugs are weaned off at least 8 weeks prior to Screening Visit 1).
28. Individual has an active peptic ulcer or gastrointestinal (GI) bleeding within the prior six months from consent.
29. Individual has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions.
30. Individual has polycystic kidney disease, unilateral kidney, atrophic kidney, or history of renal transplant.

E STUDY PREPARATION PROCEDURES

E.1 Investigator/Investigation 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, co-investigators (if applicable), and all key site staff must be willing to provide his/her curriculum vitae (CV).
- Investigational site must be willing to comply with the Clinical Investigation Plan and data collection requirements, including timely reporting Adverse Events and Device Deficiencies (Section F.13).
- 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 to refer to an Institutional Review Board (IRB), Ethics Committee (EC), Medical Ethics Committee (MEC), Head of Medical Institution (HOMI), Human Research Ethics Committee (HREC), or 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, 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 enough information to identify 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 must 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 the 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 per EC/IRB requirements.

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 the Declaration of Helsinki 2013, the latest version of international standard ISO 1415520 ('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 ISO1415520, 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 Device Regulations, SOR/98-282.

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 the 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, and (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
- Laboratory certificate and 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 (US, Canada, 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 (if applicable), all remaining investigational devices must be returned to Medtronic.

The Symplicity Spyral™ catheter and Symplicity G3™ 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

Medtronic will only allow shipment of investigational devices/products to the investigational site or investigator, after the Clinical Study Manager or designee has declared the investigational site ready to start the clinical study.

Shipment of the device/product should be requested through a representative of Medtronic. Medtronic registers the number of used investigational devices and will only ship additional investigational devices to the investigational site in case a substantial number of the previously shipped devices have been used and the CRFs have been received.

E.6.2 Storage and handling of investigational devices/products

Investigational devices/products or products provided by Medtronic 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 explant and 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:

For Symplicity G3™ generators:
Medtronic CardioVascular
7611 Northland Drive
Brooklyn Park, MN 55428
Tel: +1 800-433-4311

For Symplicity Spyral™ catheters:
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 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 informed consent must be obtained prior to the 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 3 and Table 4. A flowchart depicting the study design overview is provided in Figure 12. If subjects typically take their antihypertensive medications in the morning, it is recommended that study visits occur in the morning. If subjects typically take their antihypertensive medications in the afternoon, it is recommended that study visits occur in the afternoon. The following procedures will be followed for all subjects enrolled in this study until study exit.

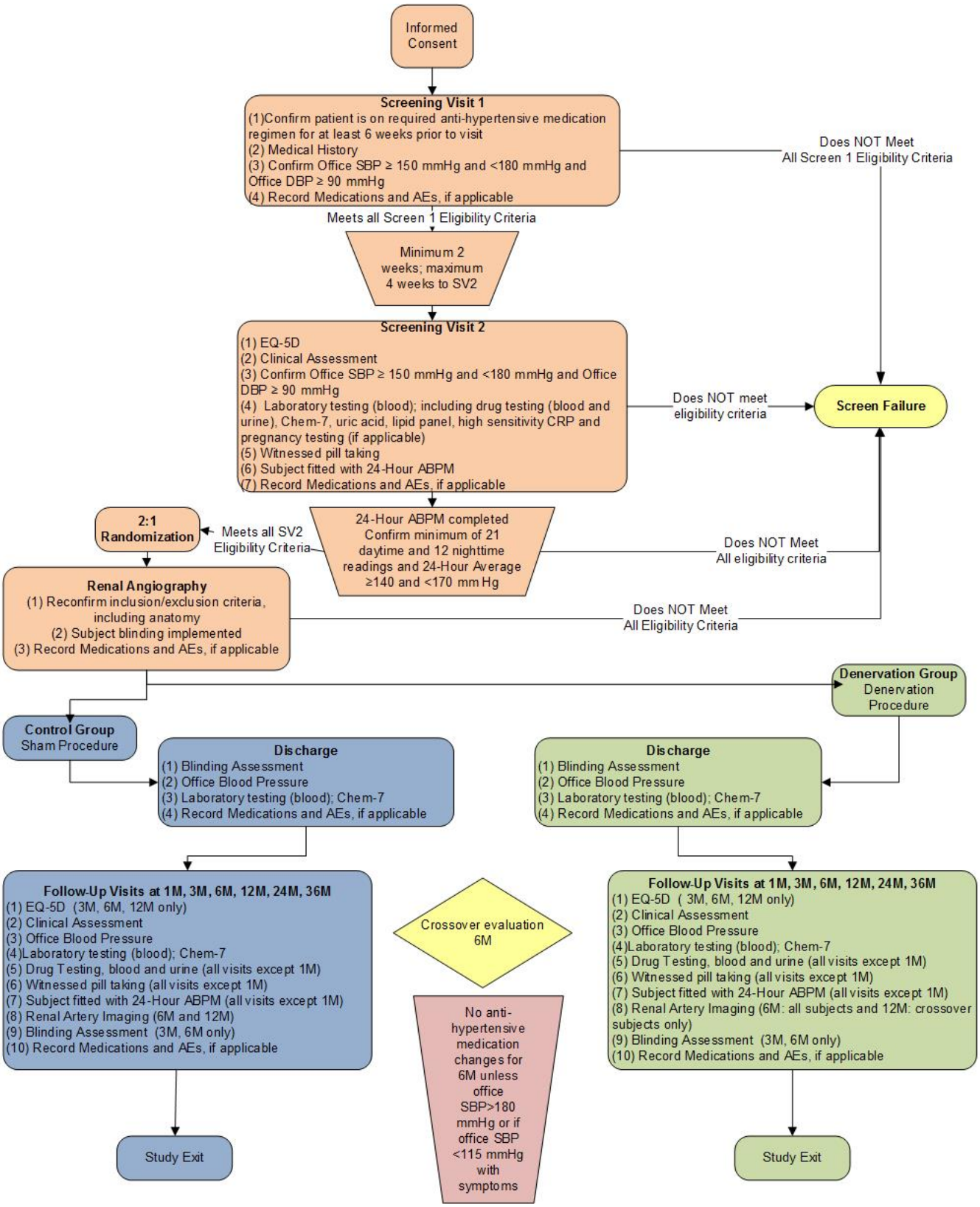

Figure 12: Study Design Overview

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. The average baseline office blood pressure value will be used for comparison with follow-up visit office blood pressure values. Subjects with an office SBP ≥ 150 and <180 mmHg and an office DBP ≥ 90 mmHg are eligible to continue to Screening Visit 2. Subjects with office SBP <150 mmHg or ≥ 180 mmHg, or an office DBP < 90 mmHg will be exited from the trial.

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

Subjects determined to not be eligible for Screening Visit 2 will be exited from the study, as described in the *Subject Exit from Trial* section of this Clinical Investigation Plan.

If the antihypertensive medication regimen is changed between Screening Visit 1 and 2 but still includes the required medications and doses, the new medication regimen must be established for a minimum of 6 weeks prior to Screening Visit 2.

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 for the study.

F.3 Screening Visit 2

Screening Visit 2 must occur within 2-4 weeks from the completion of SV1, if the subjects medication regimen did not change. 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) **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) **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 SBP ≥ 150 and <180 mmHg and an office DBP ≥ 90 mmHg are eligible to continue the screening process.

d) **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 subjects is as follows[41]:

  $$eGFR\ (mL/min/1.73\ m^2) = 194 \times (sCr)^{-1.094} \times (Age)^{-0.287} \times (0.739 \text{ if female}).$$

  Note: If eGFR ≥42 and <45 mL/min/1.73m² then patient can be retested after hydration with a single, repeat test within 48 hours.
- **hCG** 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.

e) **Witnessed pill taking prior to ABPM** will be undertaken for all ABPM measurements. 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 begin 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 applied at the conclusion of Screening Visit 2, and after witnessed pill intake, to confirm subject's baseline blood pressure. ABPM will be conducted according to the guidelines in Appendix L.7. This value will be utilized as the baseline value for calculating change in 24-hour ABPM at various time points post-randomization. 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 only allowed in case of the following:

1. If the 24-hr systolic ABPM measured is between 135 and <140mmHg or 170-175 mmHg.
2. If a valid number of readings is not obtained.
3. If there is a technical issue with the blood pressure monitor or failure to follow ABPM instructions.

If ABPM is repeated, office blood pressure, drug testing, and witnessed pill intake must be repeated on the day the ABPM is applied.

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

h) **Baseline Renal Imaging:** If a baseline Duplex Ultrasound, CT, or MRA has been collected per standard of care prior to procedure within one year from the date of Screening Visit 1, image will be upload via Medidata 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 document.

It is expected that subjects who are eligible to continue to randomization will be scheduled for the procedure 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 after 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.4 Procedure

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

2. **Renal Angiography and Blinding**

   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 heparin allergy should be initiated to maintain an ACT ≥ 250 seconds during the procedure for control and treatment groups). While the protocol mandates that subjects only be treated with up to 3 antihypertensive agents from different classes (only thiazide-type diuretic, ACE-I/ARB, dihydropyridine calcium channel blocker or beta blockers are allowed) from randomization to 6 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. However, all medications used during the procedure should be commercially available in the respective geographies and compliant with local labeling.

   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 subject is already taking aspirin on 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.

3. **Randomization and Procedure**
   Once subject's renal anatomy has been confirmed to meet eligibility criteria, the subjects will be randomized and proceed as follows based on randomization assignment:

3.1. 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 with 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, the subject will remain blinded and on the catheterization lab table for at least 20 minutes prior to the inducer sheath removal. Details of blinding procedure are described in Section C.5.

3.2. 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, oxygen saturation, and heart rate should be closely monitored both during the procedure and throughout the recovery phase from the conscious sedation administered. Investigators should 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 branch vessels between 3 mm 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 the 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 blood pressure control in the cath lab 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.

4. Post-procedure data collection requirements

After the subject has completed their procedure, 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.

4.1. 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. Due to medication already being administered during the hospital stay, witness pill intake will not be applicable for this visit. 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 daily 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.5 Follow-Up Procedures

Subjects will return for in-officefollow-up visits 1, 3, and 6 months (± 14 days) post-procedure to complete follow up visits. Subjects will additionally return at 12, 24, and 36 months (± 30 days) post-procedure to complete follow up visits. In case of a crossover, subjects will return for in-office visits at 1, 3, 6, 12, 24 and 36 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 may not be completed with an in-home visit:
    - Renal Artery Imaging:
        - Make every effort to schedule in-person renal artery imaging as soon as possible.
        - When possible, 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 study site
    - Renal Artery Imaging:
        - Make every effort to scheduled 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 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 randomized are listed below and 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-randomization visits to measure health outcomes.

b) **Clinical Assessment** will be conducted at all post-randomization 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.

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

d) **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.

- **Drug testing (urine/blood)** to ensure prescribed medications are present in the subject's system (at 3 ,6, 12, 24 and 36-month follow-up). 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.

e) **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
- **Twelve (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.

f) **Renal Artery Imaging** will be performed at the 6-month post-procedure visit to assess if renal artery stenosis is suspected. A renal duplex ultrasound (DUS) will be obtained at 6-months and submitted to the DUS Core Laboratory. If the DUS is determined to be nondiagnostic, a repeat DUS, MRA, CTA 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/CTA Core Laboratories, an angiogram must be obtained and submitted to the Angiographic Core Laboratory.

- A renal 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 30 days of their 6-month follow-up visit, a renalDUS is required.

- The 12-month renal CTA or MRA will be required from the treatment and crossover groups only. 12-month imaging is not required for control subjects who do not crossover. If the CTA or MRA 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 visit 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. 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.

g) **Witnessed pill taking prior to ABPM** will be undertaken for all ABPM measurements. 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.

h) **24-hour Ambulatory Blood Pressure Monitoring** will be applied at the conclusion of the 3-month through 36-month follow-up visits post-procedure according to the guidelines in Appendix L.7. A repeat ABPM will be allowed in the event of technical issues, if ABPM guidelines were not followed or if the minimum required number of daytime and nighttime readings is not obtained. If ABPM is repeated, office blood pressure, drug testing and witnessed pill intake must be repeated on day the ABPM is applied.

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

j) **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.6 Crossover Procedures

Control subjects may crossover to receive renal denervation therapy after completing their 6 month follow-up visit. For the subjects who have already completed their 6-month visit at the time crossover procedures are available per protocol version 7.0, the decision to crossover must take place at their next in-person visit (6, 12, 24 and 36-month follow-up or Unscheduled visit). All subjects will have 30 days from that visit to undergo the crossover procedure. Subjects that are more than 30 days from 6, 12, 24 or 36-month or Unscheduled visit, must complete a crossover baseline visit prior to having the crossover renal denervation procedure. To crossover, the required baseline data must be collected, and the subject cannot meet any of the anatomical or eGFR exclusion criteria. Crossover subjects will undergo follow up visits at 1, 3, 6, 12, 24 and 36 months post-procedure. Subjects who do not meet required eligibility for crossover on the day of the procedure will undergo follow- up visits according to their original follow-up schedule. Crossover procedures will be offered once and will not be available at a later time if it was declined by the control subject 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) **EQ-5D:** The Euro-Qol 5D (EQ-5D) will be administered.

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

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

d) **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) (if not already collected at SV2):** total cholesterol, HDL, LDL, and triglycerides, as well as high sensitive-C reactive protein tests are indented 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) (if not already collected at SV2):** This test is intended to potentially identify a marker for the renal denervation therapy responder.
- **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

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

f) **Witnessed pill taking prior to ABPM** will be undertaken for all ABPM measurements. 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.

g) **24-hour Ambulatory Blood Pressure Monitoring** will be conducted to evaluate the subject's ambulatory blood pressure according to the guidelines in Appendix L.7. Witnessed intake of antihypertensive medications should be documented as per section F.5.h. 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, drug testing, and witnessed pill intake 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, 24 and 36-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 administered at the 3, 6, 12, 24 and 36-month post-procedure visits to measure health quality of life outcomes.

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

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

d) **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.
- **Drug testing (urine/blood)** to ensure prescribed medications are present in the subject's system (at 3 ,6, 12, 24 and 36 months follow-up post crossover). 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.

e) **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 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.

f) **Renal Artery Imaging** will be performed at the 6-month post-crossover procedure visit to assess if renal artery stenosis is suspected. A renal duplex ultrasound (DUS) will be obtained at 6-months and submitted to the DUS Core Laboratory. If the DUS is determined to be nondiagnostic, a repeat DUS, MRA, CTA 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/CTA Core Laboratories, an angiogram must be obtained and submitted to the Angiographic Core Laboratory.

- The 12-month post-crossover renal CTA or MRA will be required. If the CTA or MRA is determined to be nondiagnostic, a repeat DUS, MRA, CTA 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.

  - 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.

g) **Witnessed pill taking prior to ABPM** will be undertaken for all ABPM measurements. 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.

h) **24-hour Ambulatory Blood Pressure Monitoring** will be conducted at the 3, 6, 12, 24 and 36-month post-procedure follow-up visits to evaluate the subject's ambulatory blood pressure according to the guidelines in Appendix L.7. Witnessed intake of antihypertensive medications should be documented as per section F.5.h. 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, drug testing, and witnessed pill intake 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.

For control subjects that the investigator considers to be at goal blood pressure prior to the crossover procedure and who undergo renal denervation, it is recommended that at the one month visit following the cross-over renal denervation procedure the site attempt to reduce either the antihypertensive medication dose and/or the number of prescribed antihypertensive drugs to determine whether the subject's blood pressure will remain at goal following this change. If the subject remains below goal one month later after this change, the recommendation is to continue to reduce dose or number of prescribed antihypertensive medications on a monthly basis during follow-up to determine the minimum antihypertensive prescriptions and dose needed to maintain the blood pressure goal. Visits that are not already scheduled (2, 4 and 5-month visits) will be documented under an Unscheduled Visit CRF.

F.7 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.8 Antihypertensive medication escape criteria

Antihypertensive medication changes will not be allowed up to the 6-month follow-up visit, unless the following occurs:

- In the event a subject's office SBP $\geq$ 180 mmHg from randomization up to the 6-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 antihypertensive medication regimen may be changed per the study investigator's discretion.
- In the event a subject's office SBP < 115 mm Hg and is associated with symptoms of hypotension, the antihypertensive medication regimen may be changed and other therapy administered per the investigator's discretion.

Office blood pressures conducted according to Appendix L.7 must be conducted prior to the medication change. If the subject or another physician changes medications without first consulting the investigator, the investigator must evaluate the reason for the medication change and document any adverse events, symptoms, or blood pressure measurements leading to the change and determine if it is an appropriate prescription. If the medication change was made without proper justification, the investigator should consider putting the patient back on baseline medications/doses. All efforts should be made to obtain an ABPM and Chem-7 panel prior to changing the subject's antihypertensive medication regimen. A

subject must meet the escape criteria and have medication changes in response to be considered an escape subject.

F.9 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 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.10 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 trained study personnel. A personal user ID and access code will be provided by the sponsor when all required documentation has been received. 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:

- 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 3: Schedule of Testing for All Subjects (See *Table 4* for Crossover Subjects' Testing)

1 month (30 days): 16-44 days, 3 months (90 days): 76-104 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 (M=months ± 14 days for 1M, 3M and 6M visits, months ± 30 days for 12M-36M visits)						
Required Assessments	**SV1**	**SV2**	**Procedure**	**Prior to Discharge**	**1M**	**3M**	**6M**	**12M**	**24M**	**36M**
Medical History	X									
Clinical assessment		X			X	X	X	X	X	X
Renal Denervation or Sham Procedure			X							
Office Blood Pressure according to guidelines in Appendix L.7	X	X		X	X	X	X	X	X	X
24-Hour ABPM according to guidelines in Appendix L.7		X				X	X	X	X	X
Witnessed pill taking		X				X	X	X	X	X
Blood tests (uric acid, lipid panel and high sensitivity CRP[6])		X								
Blood Tests (Chem-7)[3]		X		X	X	X	X	X	X	X
Serum or Urine Pregnancy Test		X								
Drug testing		X				X	X	X	X	X
Renal Artery Imaging - Angiogram			X							
Renal Artery Imaging – Duplex Ultrasound		X[4]					X[1]	X[5]	(X)[5]	(X)[5]
Blinding Assessment for Subjects and Assessors				X		X	X			
EQ-5D		X				X	X	X	X	X
Mortality Assessment[2]					X	X	X	X	X	X
Medication Review and Event Review	All adverse events (AE) and all medication review After 12 months, previously reported AEs will need to be reviewed and updated as needed								Serious AEs and all medication review	

[1] DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CTA 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 if crossover is completed within 30 days of 6M visit.

[2] Conduct if follow-up missed.

[3] Bicarbonate will not be measured for subjects enrolled in Japan and Europe.

[4] Submit baseline duplex ultrasound, CTA, or MRA if obtained per standard of care prior to procedure within one year from the date of screening visit 1.

[5] CTA/MRA required as first line imaging modality at 12M (and 24M and 36M as applicable). For treatment and crossover subjects only: 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 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.

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

Table 4: Schedule of Testing for Crossover Subjects

	Post-Procedure (M=months ± 14 days for 1M, 3M and 6M visit, months ± 30 days for 12M-36M visits)								
1 month (30 days): 16-44 days, 3 months (90 days): 76-104 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	**Baseline[5]**	**Renal Denervation**	**Prior to Discharge**	**1M**	**3M**	**6M**	**12M**	**24M**	**36M**
Clinical assessment	X			X	X	X	X	X	X
Blood Tests (Chem-7)[3]	X		X	X	X	X	X	X	X
Blood Tests (uric acid, lipid panel, and high-sensitivity CRP)[6]		X (prior to procedure)[5]							
Office Blood Pressure according to guidelines in Appendix L.7	X		X	X	X	X	X	X	X
Serum or Urine Pregnancy Test		X (prior to procedure)[5]							
Witnessed pill taking	X				X	X	X	X	X
24-Hour ABPM according to guidelines in Appendix L.7	X				X	X	X	X	X
EQ-5D	X				X	X	X	X	X
Renal Denervation		X							
Renal Artery Imaging - Angiogram		X							
Renal Artery Imaging						X[1]	X[4]	(X)[4]	(X)[4]
Drug Testing	X				X	X	X	X	X
Mortality Assessment[2]				X	X	X	X	X	X
Medication Review, Event Review	All adverse events (AE) and all medication review After 12 months, previously reported AE's 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, CTA 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.

[2] Conduct if follow-up visit missed

[3] Bicarbonate will not be measured for subjects enrolled in Japan and Europe

[4] 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 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.

[5] If not already collected at previous follow up visits (within 30 days of crossover procedure).

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

F.11 Role of the 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.12 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 must 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.13 Adverse events and device deficiencies

F.13.1 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 an error use 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 functionincluding chronic diseases, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) 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: 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.13.2 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 6 reporting requirements. AEs will be followed until the event has resolved or study completion, whichever comes first. (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).

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 mm Hg without producing symptoms suggestive of hypotension
- Unavoidable AEs (see Table 5)

Table 5: Unavoidable Adverse Events

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

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

Onset of any events listed in Table 5 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 until 12 months. After 12 months, only Serious Adverse Events (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 6 for the event reporting timeframe requirements. For Adverse Events that require immediate reporting (see Table 6), 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 (see Table 6). 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.13.3 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 3.15)*. Device deficiencies include malfunctions, use errors, and inadequacyin 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 6). Initial reporting may be done by will be done on the eCRF by completing as much information as is available. The Device Deficiency eCRF must be "saved as Complete" in the Remote Data Capture (RDC) system to ensure it is reported to Medtronic as soon as possible.

F.13.4 Adverse Event Reporting Requirements

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

Table 6: 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 requirements, but not later than within 10 working days after the investigator first learns of the event. **In 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 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. **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.	**Regulatory authorities (other than Canada and 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 Canada:** Medtronic will adhere to the Medical Devices Regulations, SOR/98-282. Mandatory Problem Reporting Sections 59-61. **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.
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. **In Canada:** As required by Clinical Investigational Plan. (Section F.13.4)	**Regulatory authorities:** Reporting timeframe as per local requirement.

Table 6: Adverse Event reporting requirements

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. **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 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 Post Market Release (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.	**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 requirement, but not later than within 10 working days after the investigator first learns of the event. **In Canada:** As required by the Clinical Investigation Plan (Section F.13) **In Australia:** As required by Clinical Investigation Plan (Section F.13) **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.	**Regulatory authorities (other than Australia):** Reporting timeframe as per local 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.
EC/IRB: Reporting timeframe as per local EC/IRB requirement.	**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. **In Canada:** As required by the Clinical Investigation Plan	**Regulatory authorities (other than Australia):** Reporting timeframe as per local 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.
EC/IRB: Submit to EC/IRB per local reporting requirement.	**EC/IRB:** Reporting timeframe as per local EC/IRB requirement.
Regulatory Authority: As per local reporting requirement	

Table 6: Adverse Event reporting requirements

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:** Device Deficiencies that have resulted in any of the consequences characteristic of a SADE on the patient, the user, or any person, or could do so where it could 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 Medtronic Device Regulations, SOR/98-282, Mandatory Problem Reporting Section 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.
Regulatory Authority	As per local reporting requirement.
EC/IRB	Submit to EC/IRB per local reporting requirement.

F.13.5 Data Safety Monitoring Board and Clinical Events Committees

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.13.6 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.14 Subject accountability

F.14.1 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.14. 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.14.2 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 changes, 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. (This visit does not have to be before 10:30 a.m.) 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 AE eCRF (if applicable). If the subject returns for another reason, this will not need to be documented.

F.14.3 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 and 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 should ask for the subject's permission to follow his/her status outside the clinical study.

F.14.4 Subject Exit from Trial

There are several scenarios in which a subject may exit the study. Table 7 details how the data will be handled for each scenario.

Table 7: 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, completed crossover procedure and completes the study requirements	Through 3-year follow-up

F.15 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 Trial 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.15.1 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 (if applicable) 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, 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.15.2 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 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 and 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 will 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
- randomized patient did not meet inclusion/exclusion criteria
- randomization processes not followed
- CIP required testing and/or measurements not done or incorrectly done
- subject 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 any particular investigational center or investigator 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 investigational site.

F.15.3 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 eCRFs and in all other required reports. Data reported on the eCRFs 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 eCRFs. eCRFs shall be signed off 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 eCRFs. Upon completion of an eCRF the investigator shall sign the CRF in a timely manner. If a change is made to an already signed eCRF, the investigator shall re-sign this eCRF.

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

eCRFs are recommended to be entered into the RDC system within 10 days of the completion of the protocol-specified follow-up visit, or sooner if 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 will 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 centres 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 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 performed by Medtronic's technical support staff on an annual basis.

In Japan, monitors will 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, if applicable.

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 discontinuation, by sponsor or by withdrawal of IRB/EC or local regulatory body approval, of an investigation before completion. This is possible for the entire study, all centers in a country, or 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 entire study, all centers in a country or a single center. In case of 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 Subject follow-up in case of termination

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 up on, 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 (if 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. A crossover 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 the 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 trial 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.

RDN vs. control arms will be compared out to 6-months post randomization prior to the crossover procedure. Statistical comparisons between RDN and control 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 9.2 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 Statistical Analysis Plan (SAP) for this study.

RDN vs. Crossover vs. Non-Crossover groups will be compared out to 36 months post-procedure.

Analysis Sets

a. Intent-to-Treat (ITT): All randomized subjects, analyzed according to their randomized treatment. Subjects who meet the antihypertensive medication escape criteria (Office SBP>180 or <115 associated with symptoms of hypotension or safety concern requiring medication changes) will be analyzed using Last Observation Carried Forward (LOCF) for their blood pressure measurements.

b. Modified Intent-to-Treat (modified ITT): All randomized subjects, analyzed according to their randomized treatment. Subjects who meet the antihypertensive medication escape criteria (Office SBP>180 or <115 associated with symptoms of hypotension or safety concern requiring medication changes) 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, 3-months, and 6-months
    2. Exclude subjects with protocol deviation code 101 (consent not obtained)
    3. Exclude subjects who do not meet the following Inclusion criteria
        - Inclusion: Individual has an office systolic blood pressure (SBP) ≥ 150 mmHg and <180 mmHg and an office DBP ≥90 mmHg measured at Screening Visit 2, according to the guidelines in Appendix L7.
        - Inclusion: Individual has a 24-hour ABPM average SBP ≥140 and < 170 mmHg measured at Screening Visit 2, according to guidelines in Appendix L7.
    4. Exclude subjects who meet the following Exclusion criteria
        - Exclusion: Individual has undergone prior renal denervation
        - Exclusion: Individual has renal artery anatomy that is ineligible for treatment
    5. Exclude subjects meeting the antihypertensive medication escape criteria (Office SBP>180 OR <115 associated with symptoms of hypotension or safety concern requiring medication changes).
    6. 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.

H.2 Primary Safety Objective

Medtronic is using a performance goal approach to analyze the primary safety endpoint as defined in section C.2.1. 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 binomial test was used for the sample size calculation for the primary safety endpoint hypothesis.

In other words, the primary safety endpoint hypotheses 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 patients as shown in Table 8 below to ensure 253 patients treated with the Symplicity Spyral catheter (including branch treatment) are available for analysis. The first consecutively enrolled 253 subjects with evaluable safety data from the sources in Table 8 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. The primary safety endpoint analysis will only be performed once using the first 253 subjects as detailed in this section. We will continue to report safety outcomes for all study subjects under secondary safety objectives

Table 8: 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 secondary safety endpoints defined in section C.2.2. will be analyzed as follows:

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).

RDN vs. control arms will be compared out to 6-months post randomization prior to the crossover procedure. Fisher's exact test will be used to perform statistical comparisons between the randomized groups.

RDN vs. Crossover vs. Non-Crossover groups will be compared out to 36 months post-procedure for the RDN, Non-Crossover groups and Crossover groups using chi-square tests for categorical data and ANOVA for continuous data.

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 50 subjects will provide a 95% confidence interval of approximately (0.5%, 13.7%) using the exact method (calculated using an event rate of 2/50=4%).

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 6-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 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 $t =$ 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 of H_a 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, the prior data, 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 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. We intend to use the same enrollment criteria for the prior and prospective 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.

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.4.1 Primary Efficacy Endpoint Operating Characteristics

Simulations were performed to assess operating characteristics for the primary efficacy endpoint and are presented in the two tables below. Eight thousand trial simulations were used to estimate the power and 15000 simulations to estimate the type I error. The overall power for the primary efficacy endpoint from Table 10 is 96%, with a one-sided type I error rate of 0.038.

Table 9: Simulation Parameters for Primary Efficacy Endpoint

Prior Baseline Adjusted Treatment Arm Mean/SE	-8.85 / 1.75 mmHg
Prior Treatment Arm N	36
Prior Baseline Adjusted Control Arm Mean/SE	-1.80 / 1.75 mmHg
Prior Control Arm N	36
Maximum Prior Patients	36 + 36 = 72
Prospective Study Expected Treatment Difference	5.0 mmHg
Prospective Study Treatment Arm Mean/SD	-6.8 / 12 mmHg
Prospective Study Control Arm Mean/SD	-1.8 / 12 mmHg
Weibull Discount Function Parameters	Shape: $k = 3$, Scale: $\lambda = 0.25$

Table 10: Study Operating Characteristics for Primary Efficacy Endpoint

Trial Success Rate (Power)	96%
Type I Error	0.038
First Interim Look N	N=110 evaluable (130 randomized)
Power at First Interim Look	83%
Second Interim Look N	N=149 evaluable (175 randomized)
Power at Second Interim Look	91%
Maximum Study Size	N=221 evaluable (260 randomized)
% of Simulations that Stop for Futility	1.71%

H.5 Secondary Efficacy Objectives

The secondary efficacy endpoints defined in section C.2.2. will be analyzed as follows:

RDN vs. control arms will be compared out to 6-months post randomization, prior to the crossover procedure. Statistical comparisons will be performed 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 RDN and control arms will be presented.

RDN vs. Crossover vs. Non-Crossover groups will be compared out to 36 months post-procedure for the RDN, Non-Crossover groups and Crossover groups using chi-square tests for categorical data and ANOVA for continuous data.

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 applied to all continuous secondary endpoints.

The secondary efficacy analyses will be presented for all the study populations defined in section H1.

H.6 Additional Objectives

The following additional analyses will be conducted:

- Quality of Life (QOL) EQ-5D measures.
- Antihypertensive medication usage throughout the study, including escape patients and subjects with medication changes within 6-month follow-up.
- 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.
- Medication adherence will be assessed using results from drug testing. In addition, we will perform analyses to evaluate the effect of medications adherence on BP.
- Analyses looking at long term imaging will be performed.
- COVID-19 - In accordance with FDA guidance document "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic" [8], we will perform additional analyses

to assess the effect of the COVID-19 pandemic on the study outcomes as described in the statistical analysis plan.

RDN vs. control arms will be compared out to 6-months post randomization, prior to the crossover procedure. Statistical comparisons will be performed 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 RDN and control arms will be presented.

RDN vs. Crossover vs. Non-Crossover groups will be compared out to 36 months post-procedure for the RDN, Non-Crossover groups and Crossover groups using chi-square tests for categorical data and ANOVA for continuous data.

Changes in blood pressure measurements from baseline to follow-up within each group will be assessed using paired t-tests. Two-sided 95% confidence intervals of the mean change from baseline will also be presented for each group.

These additional analyses will be presented for the ITT study population defined in section H1.

H.7 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.8 Subgroup Analyses

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

- Female vs. male gender
- Age at baseline <65 vs. ≥ 65 years
- BMI by tertiles (kg/m^2)
- Type 2 diabetics vs. non-diabetics
- Current smokers vs. former smokers vs non-smokers
- Baseline eGFR <60 vs. ≥60 mL/min/1.73 m^2
- Obstructive sleep apnea yes vs. no
- US vs. OUS subjects
- US African American vs. US non-African American subjects
- OUS 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 yes vs. no
- Orthostatic tachycardia at baseline yes vs. no
- Baseline plasma renin activity <0.65 vs. ≥0.65 (ng/mL/h)
- Baseline aldosterone-renin ratio by tertiles
- Baseline aldosterone by tertiles (ng/dL)
- Number of ablations performed by tertiles (RDN arm only)
- Total number of ablations performed in branch vessels by tertiles (RDN arm only)
- Total number of ablations performed in main renal artery vessels by tertiles (RDN arm only)
- Total number of 45 second ablations performed by tertiles (RDN arm only)
- Medication adherent vs. non-adherent subjects at screening visit 2 and 6 months (from urine and serum tests)

H.9 Publication Policy

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

Participating investigators and members of the 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 laboratories 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 trials. The members of the DSMB will not be investigators in the study and will be independent of Medtronic. Medtronic personnel may attend the meetings to answer questions but will not have a vote in determining the committee's recommendations.

Prior to the first DSMB review, guidelines for the identification, and evaluation of significant safety findings and/or increased frequency of events that may impact the rights, safety or welfare of 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 study Principal Investigators. Additional details on the DSMB process, meeting and data review schedule, as well as reporting expectations will be provided in the DSMB Charter.

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 for 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 H.9 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 or letter of regulatory compliance
- Any reports to EC/IRB and regulatory authority
- Source documentation
- Subject Identification log
- Subject Enrollment log
- Normal values or ranges for lab tests
- Laboratory certificates
- 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 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

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 be submitted to the Sponsor within 3 months after termination or completion of the investigation or the investigator's part of the investigation. • 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.
Deviations from Clinical Investigational Plan		
Emergency Use	Sponsor, EC/IRB, regulatory authority, as applicable by local regulations	Investigator will report deviation as soon as possible to the sponsor and EC/IRB.
Planned deviation	Sponsor, EC/IRB, regulatory authority, as applicable by local regulations	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 or letter of regulatory compliance
- Normal values or ranges for laboratory test
- Documentation for equipment maintenance and calibration
- Laboratory certificates
- 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 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.

Report	Submit to	Description
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.
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.
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 study closure 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 trial 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 Trial 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 Trial 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 SID 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 is 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 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.

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.

K REFERENCES

1. Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. *Mayo Clin Proc*. 2009;84:822-830
2. Joles JA. Koomans HA. Causes and consequences of increased sympathetic activity in renal disease. *Hypertension*. 2004;43:699-706
3. Mancia G, Grassi G, Giannattasio, Seravalle G. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. *Hypertension*. 1999;34:724-728
4. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet*. 2009;373:1275-1281
5. Coruzzi P, Musiari L, Mossini GL, Ceriati R, Mutti A. The renin-aldosterone system and renal function in kidney transplantation. *Clin Nephrol*. 1994;41:225-229
6. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension*. 2011;57:911-917
7. Symplicity HTN-2 Investigators , Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 study): A randomised controlled study. *Lancet*. 2010;376:1903-1909
8. Krum H, Schlaich MP, Böhm M, Sobotka PA, Mahfoud F, Rocha-Singh K, Katholi R, Esler MD. Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet.* 2014;383:622–629.
9. Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, Mahfoud F, Schlaich MP. Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the Symplicity HTN-2 randomized controlled study. *Eur Heart J.* 2014;35:1752–1759.
10. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370:1393-1401.
11. Bakris GL, Townsend RR, Flack JM, et al. SYMPLICITY HTN-3 Outcomes: Results at Twelve Months. *J Am Coll Cardiol* 2015 in press.
12. Böhm M, Mahfoud F, Ukena C et al. The First Report of the Global SYMPLICITY Registry on the effect of Renal Artery Denervation in Patients with Uncontrolled Hypertension. *Hypertension* 2015 in press.
13. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, Ewen S, Tsioufis K, Tousoulis D, Sharp AS, Watkinson AF. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. The Lancet. 2017 Aug 28.

14. Walton, T. Renal artery denervation with a new simultaneous multielectrode catheter for treatment of resistant hypertension: 6-month safety results from the SYMPLICITY Spyral First-in-Man Study. Abstract presented at: EuroPCR conference; 2014; Paris, France 2014
15. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR, Kolodgie FD, Virmani R, Joner M. Anatomic assessment of sympathetic peri-arterial renal nerves in man. *J Am Coll Cardiol*. 2014;19;64:635-643
16. Tzafriri AR, Mahfoud F, Keating JH, Markham PM, Spognardi A, Wong G, Fuimaono K, Böhm M, Edelman ER. Innervation patterns may limit response to endovascular renal denervation. *J Am Coll Cardiol*. 2014;64:1079-1087
17. Mahfoud F, Edelman ER, Böhm M. Catheter-based renal denervation is no simple matter. lessons to be learned from our anatomy? *J Am Coll Cardiol*. 2014;64:644-646
18. Pekarskiy S, Baev A, Mordovin V, Ripp T, Semke G, Sitkova E, Krylov A, Popov S. Low efficacy of renal denervation as a result of anatomically inadequate operative technique Moderated poster presented at: European Society of Cardiology (ESC) Conference; 2014; Barcelona, Spain 2014.
19. Plehn A. First experience with a new renal denervation device and technology: the Spyral device. *Confluence* 8, 2014
20. White WB, Weber MA, Sica D, Bakris GL, Perez A, Cao C, Kupfer S. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. Hypertension. 2011;57:413–420
21. "Recommendations." ICMJE | Recommendations, www.icmje.org/recommendations/
22. "GPP2." The International Society for Medical Publication Professionals, www.ismpp.org/gpp2.
23. Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J; National High Blood Pressure Education Program Coordinating Committee. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 2002; 288:1882-1888
24. Law MR, Morris JK, Wald NJ. Use of Blood Pressure Lowering Drugs in the Prevention of Cardiovascular Disease: Meta-analysis of 147 Randomised Studies in the Context of Expectations from Prospective Epidemiological Studies. *BMJ*. 2009;338:b1665
25. Schlaich MP, Sobotka PA, Krum H, Whitbourn R, Walton A, Esler MD. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. *Hypertension*. 2009;54:1195-1201
26. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819-823
27. Brunner-La Rocca HP, Esler MD, Jennings GL, Kaye DM. Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure. *Eur Heart J*. 2001;22:1136-1143
28. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A. Plasma norepinephrine, plasma renin activity, and congestive heart failure. Relations to survival and the effects of therapy in V-HeFT II. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87:VI40-48
29. Kaye DM, Lefkovits J, Jennings GL, Bergin P, Broughton A, Esler MD. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol*. 1995;26:1257-1263
30. Petersson M, Friberg P, Eisenhofer G, Lambert G, Rundqvist B. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. *Eur Heart J*. 2005;26:906-913
31. Brandt Mathias C, Mahfoud F, Reda S, Schirmer Stephan H, Erdmann E, Bohm M, Hoppe Uta C. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *Journal of the American College of Cardiology*. 2012;59:901-909

32. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC, Hoppe UC, Vonend O, Rump LC, Sobotka PA, Krum H, Esler M, Böhm M. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation*. 2011;123:1940-1946
33. Witkowski A, Prejbisz A, Florczak E, Kadziela J, Śliwinski P, Bieleń P, Michałowska I, Kabat M, Warchoł E, Januszewicz M, Narkiewicz K, Somers VK, Sobotka PA, Januszewicz A. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension*. 2011;58:559-565.
34. Medtronic Internal data.
35. Calhoun, et al. “Resistant Hypertension: Diagnosis, Evaluation, and Treatment: A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research.” Circulation. 2008; 117;e510-e526.
36. http://mdic.org/computer-modeling/virtual-patients/
37. T. Haddad, A. Himes, L. Thompson, T. Irony, R. Nair, " Incorporation of stochastic engineering models as prior information in Bayesian medical device trials", Journal of Biopharmaceutical Statistics, (2017) DOI: 10.1080/10543406.2017.1300907
38. J. G. Ibrahim and M.-H. Chen, "Power prior distributions for regression models," Statistical Science, (2000), 15(1) 46-60.
39. A. Gelman, J. Carlin, H. Stern and D. Rubin, Bayesian Data Analysis, Boca Raton: Chapman & Hall / CRC, 2004.
40. Whitbourn R, Harding SA, Walton A. Symplicity multi-electrode radiofrequency renal denervation system feasibility study. EuroIntervention 2015; 11:104-109.
41. Sanders, Margreet F., et al. "Renal artery and parenchymal changes after renal denervation: assessment by magnetic resonance angiography." *European radiology* 27.9 (2017): 3934-3941.
42. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocokc S, Tsioufis K, Tousoulis D, Choi JW, East C, Brar S, Cohen S, Fahy M, Pilcher G, Kauomi K. Effect of renal denervation on blood pressure in the presecent of antihypertenisve drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof of concept reandomised trial. *The Lancet.* 2015 May 23: http://dx.doi.org/10.1016/ S0140-6736(18)30951-6
43. Japanese Society of Hypertension Guidelines (JSH 2014), Hypertension Research (2014) 37, 266–278.
44. Franklin, S.S., Jacobs, M.J., Wong, N.D., L’Italien, G. J., Lapuerta, P. *Predominance of Isolated Systolic Hypertension Among Middle-Aged and Elderly US Hypertensives: Analysis Based on National Health and Nutrition Examination Survey (NHANES) III*. Hypertension. 2001;37:869-874.
45. Rapsomaniki, E., Timmis, A., George, J., Pujades-Rodriguez, M., Shah, A.D., Danaxas, S., White, I.R., Caulfield, M. J., Deanfield, J. E., Smeeth, L., Williams, B., Hingorani, A., Hemingway, H. *Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people.* Lancet. 2014;383:1899-911.
46. Townsend RR, Leonard CE, López de Nava K, et al. Utilization of antihypertensive drug classes among Medicare beneficiaries with hypertension, 2007–2009. Cardiovascular Issues. *Data Points* #8 (prepared by the University of Pennsylvania DEcIDE Center under contract no. HHSA29020050041I). Rockville, MD: Agency for Healthcare Research and Quality. 2011. AHRQ Publication No. 11-EHCO73-EF.

L APPENDICES

L.1 Names and addresses

L.1.1 List of contact persons

Coordinating investigators

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

Professor Dr. Michael Böhm
Universitätsklinikum des Saarlandes
Kirrberger Strasse 1
66421 Homburg
Germany

David Kandzari, MD
Piedmont Hospital
275 Collier Rd. NW, Suite 300
Atlanta, Georgia 30309-1711
United States

Kazuomi Kario, MD
Jichi Medical University Hospital
3311-1 Yakushiji
Shimotsuke, Tochigi, 329-0498
Japan

Raymond Townsend, MD
University of Pennsylvania Medical Center
210 White Building
3400 Spruce Street
Philadelphia, Pennsylvania 19104-5127
United States

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.

Service Provider	Contact Information	Services	Scope and Duties Entrusted
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.
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 10019 USA	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 Adherence Core Laboratory	Drug Adherence 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.

Service Provider	Contact Information	Services	Scope and Duties Entrusted
Morristown Medical Center	Cardiovascular Core Lab Morristown Medical Center 100 Madison Avenue Morristown, NJ 07960 Linda D. Gillam, MD, MPH, FACC, FAHA, FESC, FASE	MRA/CTA Core Laboratory	The MRA/CTA Core Laboratory is responsible for review and analysis of the MRA/CTA renal imaging to assess renal artery stenosis.
VasCore – The Vascular Ultrasound Core Laboratory	The Vascular Ultrasound Core Laboratory 1 Bowdoin Square Tenth Floor Boston, MA 02114 USA Michael R. Jaff, D.O., RPVI	Renal Artery Duplex Ultrasound (DUS) Core Laboratory	The DUS Core Laboratory is responsible for review and analysis of DUS renal imaging to assess renal artery stenosis.
Cytel	460 Totten Pond Rd, Suite 640, Waltham, MA 02451 USA	Statistical Programming and Data Analysis	Independent statistical data analysis and validation

L.1.2 List of participating investigation sites and investigators

A list of investigational sites and investigators will be provided separately.

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

4SQ	4 simultaneous quadrantic
ABPM	Ambulatory Blood Pressure Monitoring
ACC	American College of Cardiology
ACE	Angiotensin-converting-enzyme
ACE-I	Angiotensin-converting-enzyme inhibitors
ACT	Activated clotting time
ADE	Adverse Device Effect
AE	Adverse event
AV	Aortic Valve
AF	Atrial fibrillation
ARB	Angiotensin receptor blockers
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CEC	Clinical Events Committee
CIN	Contrast induced nephropathy
CIP	Clinical Investigation Plan
CMS	Center for Medicare and Medicaid Services
CPAP	Continuous positive airway pressure
CRF	Case Report Form
CRO	Clinical Research Organization
CTA	Computerized Tomographic Angiography
CV	Curriculum Vitae
DBP	Diastolic blood pressure
DD	Device Deficiency
DSMB	Data Safety Monitoring Board
DUS	Duplex Ultrasound
DVI-D	Digital Visual Interface
EC	Ethics Committee
eGFR	estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
ESRD	End-stage renal disease
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FIM	First in man

FMD	Fibromuscular Dysplasia
FU	Follow up
GCP	Good Clinical Practice
GI	Gastrointestinal
hCG	Human Chorionic Gonadotropin
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HOMI	Head of Medical Institution
HRED	Human Research Ethics Committee
hs-CRP	High-sensitivity c-reactive protein
HTN	Hypertension
IB	Investigator Brochure
ICD	Implantable Cardioverter Defibrillator
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IFU	Instructions for use
IPG	Implantable pulse generator
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-treat
J-GCP	Japan Good Clinical Practices
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MAE	Major Adverse Event
MDIC	Medical Device Innovative Consortium
MDRD	Modification of Diet in Renal Disease
MDT	Medtronic
MEC	Medical Ethics Committee
MI	Myocardial infarction
MRA	Magnetic Resonance Angiography
mSv	millisieverts
NSAIDs	Non-steroidal anti-inflammatory drugs
NSF	Nephrogenic systemic fibrosis
OBP	Office Blood Pressure
PCI	Percutaneous Coronary Intervention
PHI	Protected Health Information
PMDA	Pharmaceuticals and Medical Devices Agency

PMR	Post Market Release
PP	Per-Protocol
PRBCs	Packed red blood cells
PXM	Product Experience Management
QA	Quality Assurance
QOL	Quality of Life
RCT	Randomized Control Trial
RDC	Remote data capture
RDN	Renal Denervation
REB	Research Ethics Board
RF	Radiofrequency
RX	Rapid Exchange
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SID	Subject Identification Number
SNS	Sympathetic nervous system
SOP	Standard operating procedure
SV1	Screening Visit 1
SV2	Screening Visit 2
TGA	Therapeutic Goods Administration
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect

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 mm Hg, together with progressive or impending target organ damage, requiring in-patient hospitalization and typically admission to the Intensive Care Unit (ICU) (e.g., with parenteral [IV] antihypertensive medications), not related to confirmed non-adherence with medication

  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)$^{-1.094}$ x (Age)$^{-0.287}$ x (0.739 if Female)

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

Generalizability to Medicare Beneficiaries

The results of this study are expected to be generalizable to the Medicare population based on the incidences of uncontrolled hypertension and combined hypertension in patients ≥65 years old, as well as estimates of the number of elderly patients taking at least one class of antihypertensive medication.

The incidence of uncontrolled hypertension is strongly correlated with older age; 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 mmHg. Among elderly participants >75 years of age, fewer 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]

In an analysis of NHANES III data, approximately 13% of the untreated & inadequately treated (i.e., uncontrolled) hypertensive elderly population age 65 years or older were found to have combined systolic and diastolic hypertension (SBP ≥ 140mmHg, DBP ≥ 90mmHg).[44] While the combined hypertensive population comprises a smaller percentage of elderly patients relative to isolated systolic hypertension, combined hypertension is associated with as many years of life lost to cardiovascular disease in elderly patients as with isolated systolic hypertension.[45] Thus, the study of effective treatment of combined hypertension in elderly patients is expected to have relevance and benefit to the improvement of cardiovascular health of Medicare beneficiaries.

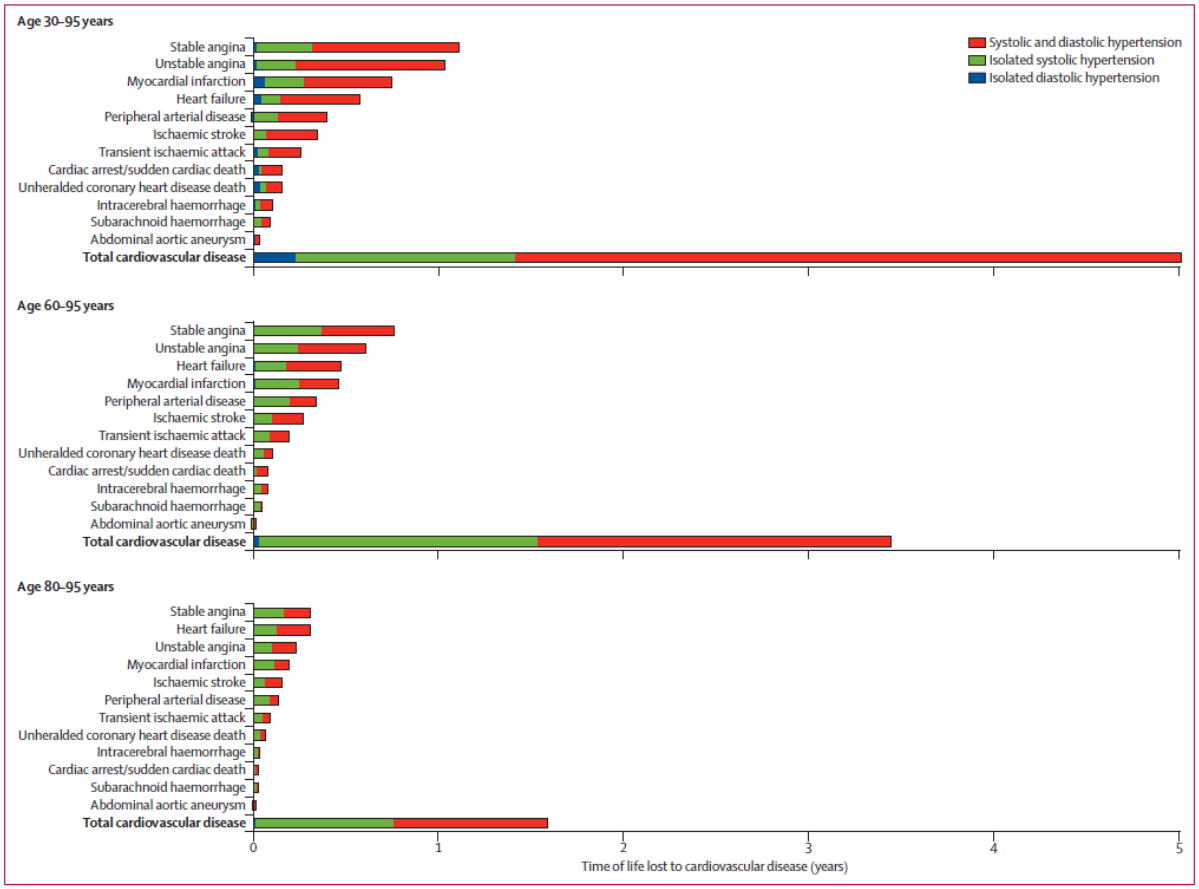

Figure 6: **Years of life lost to cardiovascular disease up to 95 years of age associated with hypertension at index ages 30, 60, and 80 years, adjusted for sex, smoking, diabetes, and total and high-density lipoprotein cholesterol**

83 098 total cardiovascular disease events occurred.

Figure 13: Rapsomaniki, et al., 2014

In a study of Medicare data between 2007 and 2009, Townsend et al reported that 87% to 88% of Medicare beneficiaries with hypertension used at least one prescription for an antihypertensive drug; as patient age increased, this percentage of Medicare beneficiaries increased (upwards to >89% for patients 85 years and over), along with the mean number of antihypertensive drug classes used by all hypertensive beneficiaries (from 1.8±1.3 to 2.0±1.2).[46] 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 65 years or older.[34]The results of this study are thus expected to be generalizable to the populations of Medicare beneficiaries with uncontrolled, combined hypertension and are prescribed at least one antihypertensive class of medication.

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 10:30 am. This does not apply to Screening Visit 1 (if 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 (OR HOLD OFF TAKING THEIR ANTIHYPERTENSIVE MEDICATION UNTIL THE OFFICE BLOOD PRESSURE MEASUREMENT IS COMPLETED IN THE CASE OF IN-HOME, VIRTUAL OR TELEPHONE VISITS). THE REQUIREMENT FOR NOT TAKING THE MEDICATION IN THE MORNING OF THE VISIT DOES NOT APPLY TO UNSCHEDULED VISITS, THE DISCHARGE VISIT OR SCREENING VISIT 1 IF THE SUBJECT SIGNED THE INFORMED CONSENT FORM AT SV1.**

A. ARM SELECTION AT SCREENING VISIT 1 ONLY

(1) The subject visit should begin before 10:30 am unless the subject normally takes their antihypertensive 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.
    - In the event systolic BP is the same on both arms, the subject should choose the 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 arm and BP cuff. The legs should not be crossed.
(5) Ensure that the BP cuff is appropriately sized (see Table 11) 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 11: 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 mm Hg apart, take one additional reading and average the last 3 consecutive measurements (measurements 2-4). If the measurements are still >15 mm Hg apart, take one additional reading and average the last 3 consecutive measurements (measurements 3-5). If the measurements are still >15 mm Hg 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 mm Hg 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 mm Hg 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.

- **ALL PATIENTS MUST BE OBSERVED SWALLOWING THEIR ANTIHYPERTENSIVE MEDICATION PRIOR TO APPLYING THE ABPM DEVICE (OR VERBALLY CONFIRMED IN THE CASE OF A PHONE VISIT).**
- **CUFF SIZE IDENTIFIED AT SCREENING VISIT 2 SHOULD BE USED FOR THE DURATION OF THE STUDY.**

(1) The subject office visit should begin before 10:30 am 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 document pill identity and observe the subject swallowing the antihypertensive medication(s) (or verbally confirmed in the case of a phone visit). 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 the 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 guidelines.

     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 ABPM Guidelines

Guidelines will be provided separately.

L.12 Serious or Unanticipated Adverse Event Report (Rush form) – *Japan only*

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

L.13 Angiographic Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.

L.14 Renal Duplex Ultrasound (DUS) Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.

L.15 Magnetic Resonance Angiographic (MRA) / Computerized Tomography (CT) Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.

L.16 Blood Core Laboratory Guidelines

Blood Core Laboratory guidelines will be provided separately.

L.17 Drug Testing Core Laboratory Guidelines

Core Laboratory guidelines will be provided separately.