CIP No: 1201
Revision: C
16 Nov 2012

EnligHTN II

IntErnational non-randomized, single arm, long-term follow-up study of patients with uncontrolled HyperTensioN

Clinical Investigation Plan (CIP)

SPONSOR

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Clinical Investigation Plan Signature Page

Study Title: EnligHTN II – Int**E**r**n**ationa**l**, non randomized, s**i**ngle arm, lon**g** term follow up study of patients with uncontrolled **H**yper**T**ensio**N**

Study Number: 1201

Study Device: EnligHTN™ Renal Denervation System

I have read and agree to adhere to the Clinical Investigational Plan and all regulatory requirements applicable in conducting this clinical study. I will provide copies of this clinical investigational plan and all pertinent information to study personnel and will discuss this information with them and ensure they are fully informed regarding the device and the conduct of the study according to other applicable regulations, to applicable laws.

_____
Site Principal Investigator Name (please print)

_____ _____
Site Principal Investigator Signature Date

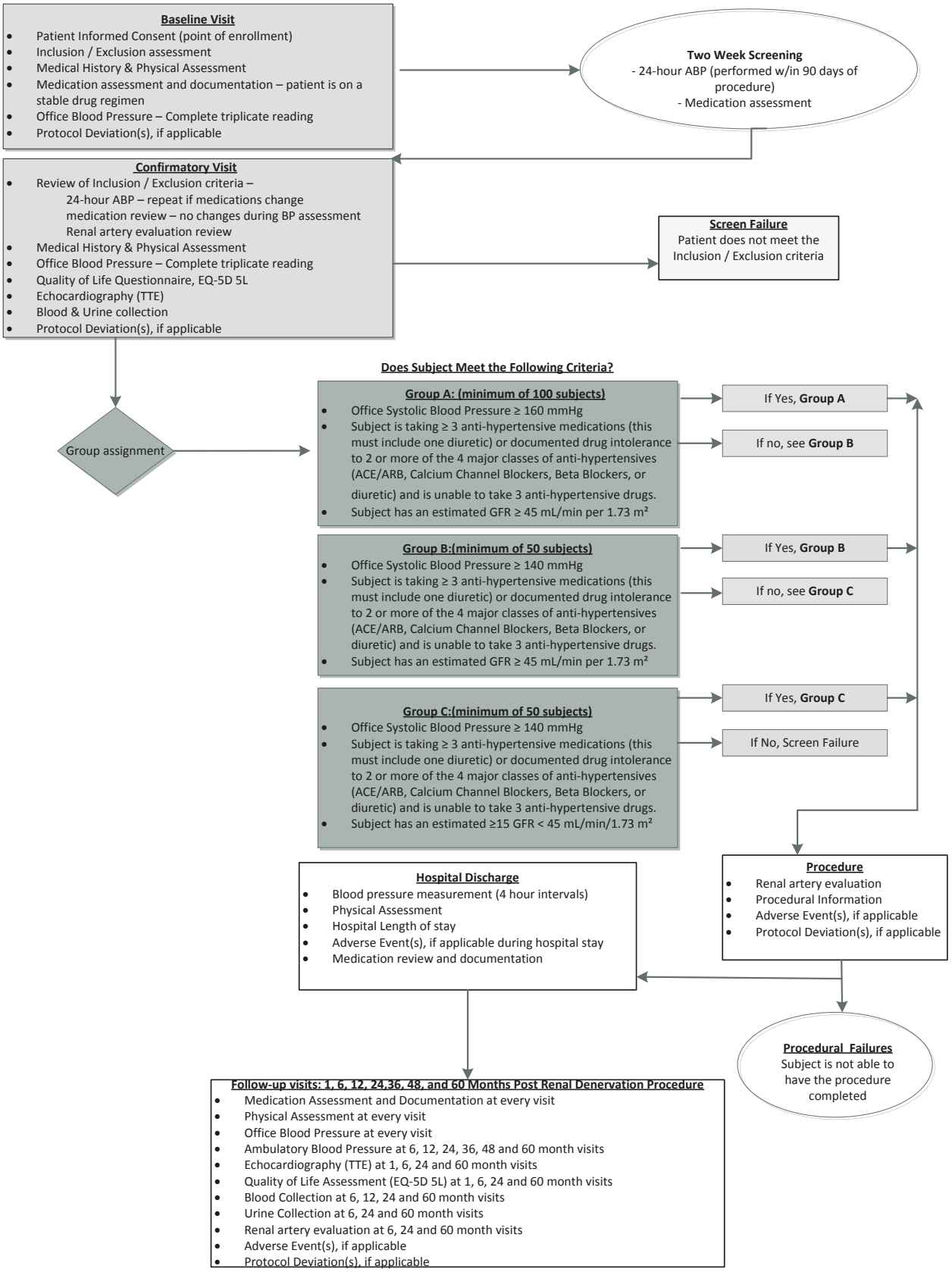
Table of Contents

1 Synopsis

Title:	Int**E**r**n**ationa**l** non-randomized, s**i**ngle-arm, lon**g**-term follow-up study of patients with uncontrolled **H**yper**T**ensio**N**
Acronym:	EnligHTN II
Purpose:	The purpose of this post market clinical investigation is to further evaluate the safety and performance of the EnligHTN™ Renal Denervation System in the treatment of patients with uncontrolled hypertension.
Objectives:	The objective of this clinical investigation will be to assess the EnligHTN™ Renal Denervation System in renal artery ablation for the treatment of uncontrolled hypertension. Primary Objective: • Mean reduction in office Systolic Blood Pressure at six (6) months across all subjects post renal denervation and within sub-groups Secondary Objectives: Safety Acute (30 days post procedure): • The assessment of peri-procedural events Midterm (6 months): • Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation • Renal function change based on eGFR Long term (2 and 5 years): • Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation • Renal function change based on eGFR BP reduction • Change in Ambulatory Blood Pressure parameters at 6 months • Change in office Diastolic Blood Pressure at 6 months • Percentage of subjects achieving office Systolic Blood Pressure < 140 at 6 month visit • Change in Office and Ambulatory Blood Pressure parameters at 12, 24, 36, 48, 60 months post denervation

Design:	This is a post market, prospective, multicenter, non-randomized, single arm study of the EnligHTN™ Renal Denervation System. Approximately 500 subjects with uncontrolled hypertension will undergo renal artery ablation at approximately 40 investigational sites located internationally and will be followed up to five (5) years post procedure.
	The clinical investigation is anticipated to start in October of 2012. Enrollment is anticipated to end in September of 2013. Subject participation will be up to five (5) years post procedure. Clinical investigation completion in 2018.
Devices used:	EnligHTN™ Renal Artery Ablation Catheter EnligHTN™ RF Generator EnligHTN™ Guiding Catheter (optional) All devices used in this investigation, have received appropriate certification (and are market released in the geographies participating in this clinical investigation).
Patient Population:	The patient population enrolled in this investigation will consist of male and female patients 18 years of age or older that meet all of the specified inclusion criteria and none of the specified exclusion criteria
Patient Screening	Patient Screening: Patients that will be treated at the investigational site will be screened by a member of the investigational team. Patients who do not meet the inclusion/exclusion criteria are not eligible to participate. Patients meeting the inclusion/exclusion criteria will be fully informed about the investigation and will be asked to participate in the investigation. A duly signed and dated, Ethics committee (EC) and Sponsor approved, Patient Informed Consent (PIC) will be obtained. A patient becomes a subject once he/she has been fully informed about the investigation, has agreed to participate, signed & dated the Patient Informed Consent (PIC) and therefore has been enrolled in the investigation.
Inclusion Criteria	• Subject is ≥ 18 years of age at time of consent • Subject must be able and willing to provide written informed consent • Subject must be able and willing to comply with the required follow-up schedule • Subject has office Systolic Blood Pressure ≥ 140 mmHg at confirmatory visit • Subject has a daytime mean Systolic Ambulatory Blood Pressure > 135 mmHg within 90 days prior to procedure • Subject has established hypertension (diagnosed ≥12 months prior to baseline) and is on a guideline based drug regimen at a stable and a fully tolerated dose consisting of ≥3 anti-hypertensive medications (including 1 diuretic), or subject has documented drug intolerance to 2 or more of the 4 major classes of anti-hypertensives (ACE/ARB, Calcium Channel Blockers, Beta Blockers, or diuretic) and is unable to take 3 anti-hypertensive drugs.
Exclusion Criteria	• Subject has significant renovascular abnormalities such as renal artery stenosis > 30% • Subject has undergone prior renal angioplasty, renal denervation, indwelling renal stents, and/or abdominal aortic stent grafts • Subject has hemodynamically significant valvular heart disease as determined by study investigator • Subject has a life expectancy less than 12 months, as determined by the

	Investigator • Subject is participating in another clinical study which has the potential to impact their hypertension management (pharmaceutical/device/homeopathic) • Subject is pregnant, nursing, or of childbearing potential and is not using adequate contraceptive methods • Subject has active systemic infection • Subject has renal arteries with diameter(s) < 4 mm in diameter • Subject has an estimated GFR <15 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula • Subject had a renal transplant or is awaiting a renal transplant • Subject has blood clotting abnormalities



Visit	Enrollment / Baseline	Confirmatory	Procedure	Discharge <72 hrs	1M ±14d	6M ±30d	12M ±60d	24M ±60d	36M ±60d	48M ±60d	60M ±60d
PIS & PIC	X										
Inclusion/Exclusion	X	X-review for changes									
Medical History	X	X-review for changes									
Office Blood Pressure	X	X		X	X	X	X	X	X	X	X
Physical Assessment	X	X-review for changes		X	X	X	X	X	X	X	X
24-h Ambulatory Blood Pressure	X-performed w/in 90 days of procedure	X-repeat if there are medication changes				X	X	X	X	X	X
Discharge Blood Pressure				X*							
***Echocardiography (TTE)		X			X	X		X			X
NYHA Assessment	X				X	X		X			X
Serum creatinine		X				X	X	X			X
Estimated GFR		X				X	X	X			X
Hemoglobin A1c		X				X					
Fasting Glucose		X				X					
Fasting Insulin		X				X					
Urine albumin-to-creatinine ratio		X				X		X			X
Medications Log	X	X-review for changes		X	X	X	X	X	X	X	X
Quality of Life questionnaire		X			X	X		X			X
Renal Artery Anatomy Evaluation		X – if not performed w/in 90 days	X			X		X			X
Pregnancy Test (urine / blood)		X									
Renal Denervation Procedure			X								
Adverse Event	**	**	**	**	**	**	**	**	**	**	**
CIP Deviation	**	**	**	**	**	**	**	**	**	**	**
Withdrawal/ Termination			**	**	**	**	**	**	**	**	X

(*) monitored every 4 hours post procedure until discharge, or for a maximum of 24 hours
(**) as applicable
(***) Echo will be performed at 6 preselected sites

2 Background

Hypertension or high blood pressure is a major risk factor for cardiovascular and cerebrovascular events.[1-3] It is responsible for approximately one half of the coronary heart disease and two thirds of the cerebrovascular disease burdens.[4] It is also the world's number one attributable risk for death. The global prevalence of hypertension has been increasing. An analysis indicated that more than one quarter (nearly one billion) of the world's adult population had hypertension in 2000. This is projected to increase to 1.56 billion affected individuals with a prevalence rate of 29% in 2025.[5] This is a major public health challenge in both economically developing and developed countries.

Previous studies showed that drug therapy may reduce the risk of major cardiovascular events by about 20% and the risk of stroke by about 40% in patients with hypertension.[6-10] However, these may not apply to all patients with hypertension. A large proportion of patients with hypertension still remains untreated or uncontrolled due to many factors.[11-12] For patients with resistant hypertension despite the use of aggressive drug therapy, which includes at least 3 anti-hypertensive drugs with a diuretic being one of these drugs, blood pressure management remains uncontrolled.[13] In the general hypertensive population, the prevalence of resistant hypertension is estimated to be about 5% to 12%. In patients with co-morbidity, such as chronic renal failure or diabetes, the prevalence of resistant hypertension is even significantly higher. [14-19] Hypertension is also mainly an asymptomatic disease, which could be difficult to have the patient understanding about the importance of complying and adhering to the lifelong drug therapy. Alternative approaches to control the blood pressure of these patients are urgently needed.[20]

The kidneys represent the central homeostatic organ regulating blood pressure and blood volume.[21] The sympathetic innervation of the kidney is implicated in the pathogenesis of hypertension through enhanced renin secretion and sodium re-absorption and reduced renal blood flow.[22-24] Renal sympathetic afferent and efferent nerves run within and adjacent to the wall of the renal artery.[25-27] Previous experimental functional studies showed that activation of the renal sympathetic nerve could cause increase and even spillover of the norepinephrine production, which results in the elevation of blood pressure, while renal denervation could reduce the norepinephrine level of up to 95%.[28-30] Sectioning of the renal afferent nerves controlled the increased sympathetic activity in the posterior hypothalamus and allowed good control of the elevated blood pressure.[31-34] In various experimental models, which include spontaneous hypertension, deoxycorticosterone-acetate-induced hypertension, obesity-induced hypertension and aortic coarctation models, the magnitude of the hypertension has been reduced and the renal blood flow has been increased during the observation period after renal denervation.[29-30,35]

Radical surgical methods for abdominal, thoracic or pelvic sympathetic denervation (radical sympathectomy) have been used to treat patients with severe or malignant hypertension more than five decades ago.[36-44] However, after the advent of modern anti-hypertensive drug therapy, radical sympathectomy was mainly reserved for non-responders of the anti-hypertensive drug therapy due to the extensive surgical procedure and technique, significant procedural time, long hospital stay (generally 2 to 4 weeks) and long recovery time (generally 4 to 8 weeks) in patients involved.

Percutaneous catheter-based methods deliver radiofrequency (RF) energy to the renal sympathetic nerves for the ablation-induced renal denervation. This minimally invasive and more localized approach allows for possibly much shorter procedural time, shorter hospital stay and shorter recovery time, which may benefit more patients with uncontrolled hypertension.

Recent clinical studies reported significant improvement of office blood pressure measurement in patients with resistant hypertension after the catheter-based renal denervation procedure (about -20/-10 mmHg, -25/11 mmHg, -23/-11 mmHg and -32/-14 mmHg at 1, 6, 12 and 24 months respectively from baseline systolic/diastolic blood pressures).[45-47,56]

Further insights into mechanisms of hypertension control through renal denervation were published in a recent case report of a 59-year old patient with long-standing uncontrolled hypertension on a multi-drug regimen.[48] The baseline renal norepinephrine spillover from both the left and right kidneys was approximately three times above the normal level, which indicated an elevated renal sympathetic neuronal efferent activity. Bilateral renal denervation resulted in a progressive and sustained improvement in the systemic blood pressure from 161/107 mmHg at baseline to 121/81 mmHg at 12 months and a decrease of the norepinephrine spillover by 48% from the left kidney and 75% from the right kidney at 1 month after the renal denervation procedure. The muscle sympathetic nerve activity as assessed by microneurography also reduced gradually to normal levels 12 months after the renal denervation procedure.

EnligHTN-I (ARSENAL) was a feasibility study to demonstrate the safety and efficacy of the St. Jude Medical Radiofrequency Renal Denervation System in the treatment of patients with resistant hypertension. This study is currently being conducted at four (4) investigational sites in Australia and Greece. Enrollment was completed on March 1, 2012 with a total of 46 patients having undergone the renal denervation procedure. Subjects will be followed for 24 months post procedure.

The one month clinical results from EnligHTN I were presented at the European Association of Percutaneous Cardiovascular Interventions, EuroPCR 2012 Congress May 15-18, 2012. Data was presented on 46 patients from four sites (60±10 years, 15 females/ 31 males) with a baseline average office Blood Pressure (BP) measurement of 176±16 / 96±14 mmHg, and an average of 4±0.6 anti-hypertensive medications. Fifteen (15) patients had a history of Diabetes Mellitus Type II. Median procedure time was 34.0 with a mean number of ablations completed on the right side of 7.7±0.8 and the left side of 7.4±1.4. One patient had the renal denervation procedure completed on the right side only due to tortuous anatomy. No vascular or renal artery complications were observed at the end of the procedure in any of the patients. At the time of discharge the average Blood Pressure measurement was 154/88 mmHg and at the one month time point the average office Blood Pressure measurement was 148/87 mmHg. The average systolic / diastolic Blood Pressure between baseline and one month was -28/-10 mmHg with 78% of the patients experiencing a ≥ 10 mmHg reduction in systolic Blood Pressure [58].

The three month clinical results from EnligHTN I were presented at the European Society of Cardiology (ESC) meeting on 28 August 2012. At the three month time point the average systolic / diastolic Blood Pressure difference between baseline and three month follow-up was -27/-10 mmHg with 80% of the patients experiencing a ≥ 10 mmHg reduction in systolic Blood Pressure. At 3 months, the mean systolic/diastolic ambulatory Blood Pressure difference between baseline and 3 months was -9.9/-5.4 mmHg.

3 Investigational Design

3.1 Purpose

The purpose of this Clinical investigation is to further evaluate the safety and performance of the EnligHTN™ Renal Denervation System in the treatment of patients with uncontrolled hypertension.

3.2 Objectives

Primary Objective

The primary objective is to evaluate a mean reduction in office Systolic Blood Pressure at six (6) months across all subjects post renal denervation and within sub-groups.

Secondary Objective

The secondary objectives are:

Safety

Acute (30 days post procedure):

- The assessment of peri-procedural events

Midterm (6 months):

- Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation
- Renal function change based on eGFR

Long term (2 and 5 years):

- Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation
- Renal function change based on eGFR

BP reduction

- Change in Ambulatory Blood Pressure parameters at 6 months
- Change in office Diastolic Blood Pressure at 6 months
- Percentage of subjects achieving office Systolic Blood Pressure < 140 at 6 month visit
- Change in Office and Ambulatory Blood Pressure parameters at 12, 24, 36, 48, 60 months post denervation

3.3 Investigational Type

This is a post market, prospective, multicenter, non-randomized, single arm study of the EnligHTN™ Renal Denervation System. Approximately 500 subjects with uncontrolled hypertension will undergo renal artery ablation at approximately 40 investigational sites located internationally and will be followed up to five (5) years post procedure.

3.4 Patient Population

The patient population enrolled in this investigation will consist of male and female patients 18 years of age or older that meet all of the specified inclusion criteria and none of the specified exclusion criteria (Section 3.5).

3.5 Patient Screening

All patients treated at the investigational site can be screened by a member of the investigational team. This team member needs to be trained on the Clinical Investigational Plan (CIP) and the task of subject screening needs to be delegated in writing to this team member by the Principal Investigator.

The patient will be given ample time to ask questions and to understand the risks of being a part of this investigation. In case the patient agrees to participate, a duly signed and dated Patient Informed Consent (PIC) will be obtained.

3.6 Inclusion and Exclusion Criteria / Point of Enrollment

A patient, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this investigation. A patient becomes a subject once he/she has been fully informed about the investigation, has agreed to participate, signed & dated the PIC and therefore has been enrolled in the investigation. (Refer to section 5.2 for the Informed Consent Process)

Once enrolled, a subject is expected to comply with the scheduled visits and required activities according to the CIP. The subject should undergo the renal denervation procedure within 30 days of the baseline visit but must be no longer than 90 days from baseline.

All subjects enrolled in the clinical investigation (including those withdrawn from the clinical investigation or lost to follow-up) shall be accounted for and documented in the Patient Identification Log, assigning an identification code linked to their names, alternative identification or contact information. Because subject privacy and confidentiality of data must be maintained throughout the clinical investigation, this log will only remain on site.

This log shall be kept up to date throughout the clinical investigation by the Principal Investigator or his/her authorized designee.

3.6.1 Inclusion Criteria

- Subject is ≥ 18 years of age at time of consent
- Subject must be able and willing to provide written informed consent
- Subject must be able and willing to comply with the required follow-up schedule
- Subject has office Systolic Blood Pressure ≥ 140 mmHg at confirmatory visit
- Subject has a daytime mean Systolic Ambulatory Blood Pressure > 135 mmHg within 90 days prior to procedure
- Subject has established hypertension (diagnosed ≥12 months prior to baseline) and is on a guideline based drug regimen at a stable and a fully tolerated dose consisting of ≥3 anti-hypertensive medications (including 1 diuretic), or subject has documented drug intolerance to 2 or more of the 4 major classes of anti-hypertensives (ACE/ARB, Calcium Channel Blockers, Beta Blockers, or diuretic) and is unable to take 3 anti-hypertensive drugs.

3.6.2 Exclusion Criteria

- Subject has significant renovascular abnormalities such as renal artery stenosis > 30%

- Subject has undergone prior renal angioplasty, renal denervation, indwelling renal stents, and/or abdominal aortic stent grafts
- Subject has hemodynamically significant valvular heart disease as determined by Study investigator
- Subject has a life expectancy less than 12 months, as determined by the Study Investigator
- Subject is participating in another clinical study which has the potential to impact their hypertension management (pharmaceutical / device / homeopathic)
- Subject is pregnant, nursing, or of childbearing potential and is not using adequate contraceptive methods
- Subject has active systemic infection
- Subject has renal arteries with diameter(s) < 4 mm in diameter
- Subject has an estimated GFR <15 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula
- Subject had a renal transplant or is awaiting a renal transplant
- Subject has blood clotting abnormalities

3.7 Procedural Exclusions

Subjects who have been enrolled in the clinical investigation and the procedure was started but do not have the EnligHTN™ Renal Denervation System enter their body, due to their anatomy, circumstances related to the procedure, or physician judgment will be classified as procedurally excluded. The reason for the procedural exclusion will be documented on the Procedural CRF. The subject will return for a 1 month follow up visit and have a physical assessment and office blood pressure completed.

3.8 Expected duration of the Investigation

The expected duration of the investigation will be approximately six (6) years.

3.9 Expected duration of each subject's participation

The expected duration of each subject enrolled in the clinical investigation will be five (5) years.

3.10 Number of subjects required to be included in the Investigation

Enough subjects will be enrolled to have approximately 500 subjects undergo the renal denervation procedure in the investigation. Procedurally excluded subjects will not count towards the expected number of treated subjects.

3.11 Estimated time needed to select this subject population

The estimated time needed to enroll the number of subjects will be approximately 8 months.

3.12 Devices Used

The EnligHTN™ Renal Denervation System is designed to deliver radiofrequency (RF) energy to the renal nerves to achieve targeted denervation. The system consists of the EnligHTN™ RF Ablation Generator (generator), the EnligHTN™ Renal Artery Ablation Catheter (ablation catheter), and the EnligHTN™ Guiding Catheter (optional).

The following market approved St. Jude Medical devices to be first used in this investigation are:

3.12.1 EnligHTN™ Renal Artery Ablation Catheter

The EnligHTN™ Renal Artery Ablation Catheter is a single use device that has an expandable electrode basket with four Platinum-Iridium (Pt-Ir) ablation electrodes. The electrodes deliver low-level radiofrequency energy to the renal arteries through a percutaneous vascular access site. The distal segment of the ablation catheter is deflectable to assist in proper basket positioning. The handle is used to actuate the expansion and relaxation of the basket, and to actuate the deflection of the ablation catheter at the distal end. The ablation electrodes and the tip are radiopaque to provide visualization under fluoroscopy.

3.12.2 EnligHTN™ RF Ablation Generator

The EnligHTN™ RF Ablation Generator delivers RF energy to the EnligHTN Renal Artery Ablation Catheter using a proprietary algorithm developed to produce a consistent, transmural ablation pattern during the renal denervation procedure.

3.12.3 EnligHTN™ Guiding Catheter (optional)

The EnligHTN™ Guiding Catheter system is comprised of two (2) components: a guiding catheter and a dilator. The guiding catheter is constructed of three (3) components: a polytetrafluoroethylene (PTFE) liner, a stainless steel braid, and a multi durometer polymer jacket. The proximal end of the catheter terminates in a hemostasis hub and a hemostasis valve. An extension tube and 3-way stopcock valve is attached to the sideport of the hemostasis hub. The distal end of the catheter terminates in a renal curve with a radiopaque marker embedded in the polymer jacket approximately 2 mm from the catheter tip. The dilator is a polymer tube with an inside diameter sized for guidewire clearance. The proximal end terminates in a snap fitting to mate with the guiding catheter hemostasis hub. The distal end is tapered to facilitate insertion through an introducer sheath.

3.13 Intended Use

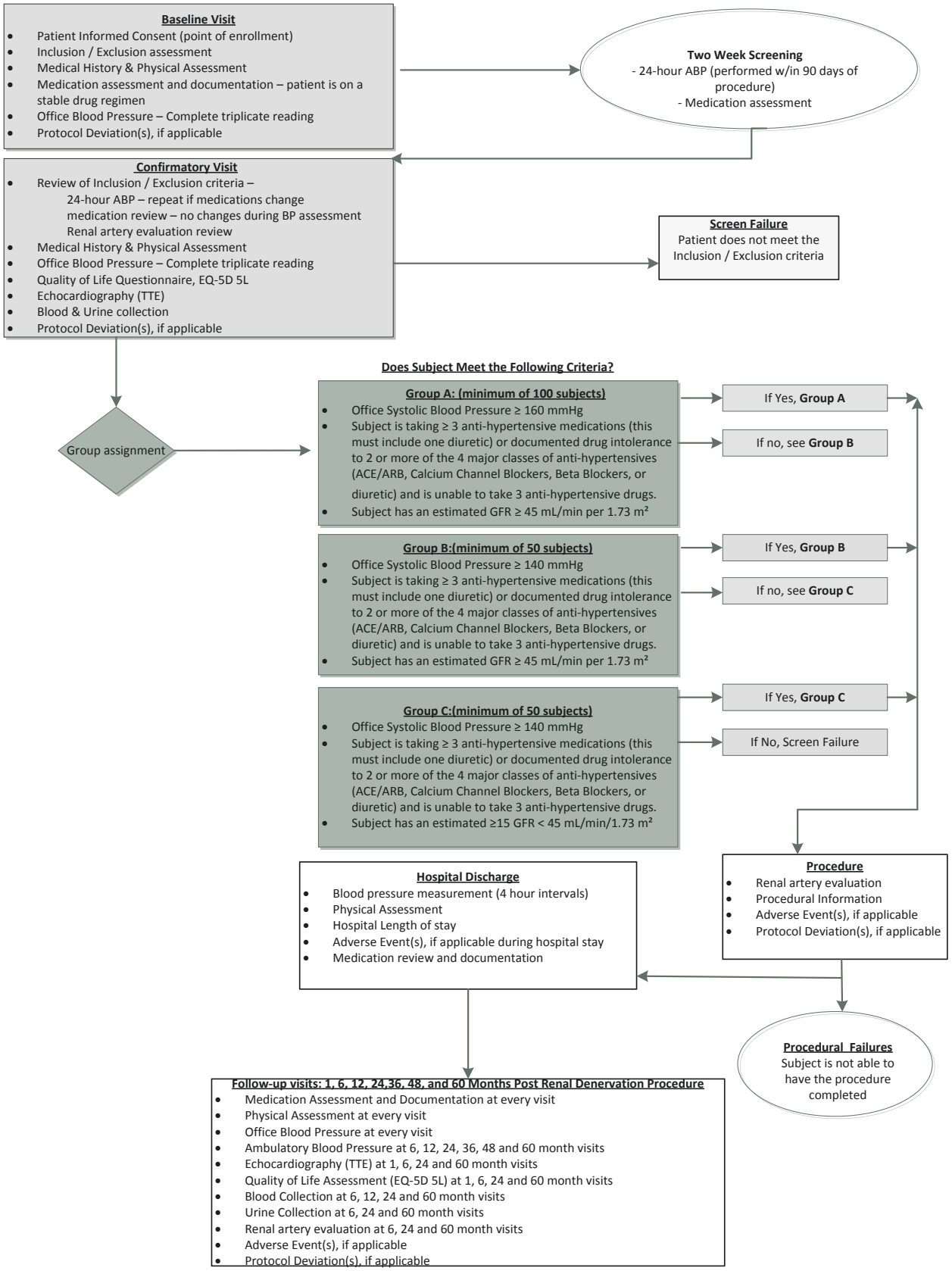
The ablation catheter is indicated for use in renal denervation procedures for the treatment of hypertension.

4 Procedures

Table 1: Data/CRF Collection

Visit	Enrollment / Baseline	Confirmatory	Procedure	Discharge <72 hrs	1M ±14d	6M ±30d	12M ±60d	24M ±60d	36M ±60d	48M ±60d	60M ±60d
PIS & PIC	X										
Inclusion/Exclusion	X	X-review for changes									
Medical History	X	X-review for changes									
Office Blood Pressure	X	X		X	X	X	X	X	X	X	X
Physical Assessment	X	X-review for changes		X	X	X	X	X	X	X	X
24-h Ambulatory Blood Pressure	X-performed w/in 90 days of procedure	X-repeat if there are medication changes				X	X	X	X	X	X
Discharge Blood Pressure				X*							
***Echocardiography (TTE)		X			X	X		X			X
NYHA Assessment	X				X	X		X			X
Serum creatinine		X				X	X	X			X
Estimated GFR		X				X	X	X			X
Hemoglobin A1c		X				X					
Fasting Glucose		X				X					
Fasting Insulin		X				X					
Urine albumin-to-creatinine ratio		X				X		X			X
Medications Log	X	X-review for changes		X	X	X	X	X	X	X	X
Quality of Life questionnaire		X			X	X		X			X
Renal Artery Anatomy Evaluation		X – if not performed w/in 90 days	X			X		X			X
Pregnancy Test (urine / blood)		X									
Renal Denervation Procedure			X								
Adverse Event	**	**	**	**	**	**	**	**	**	**	**
CIP Deviation	**	**	**	**	**	**	**	**	**	**	**
Withdrawal/ Termination			**	**	**	**	**	**	**	**	X

(*) monitored every 4 hours post procedure until discharge, or for a maximum of 24 hours
(**) as applicable
(***) Echo will be performed at 6 preselected sites



4.1 Enrollment/Baseline Visit

Prior to enrollment in the clinical investigation, site personnel will evaluate potential candidates by reviewing the patient medical records against the inclusion and exclusion criteria. It is expected that the medical records will contain adequate and accurate information to determine if the patient meets these criteria.

If a patient meets all inclusion criteria and does not meet any of the exclusion criteria, the patient shall be eligible for the investigation.

If the patient agrees to participate, the study site personnel shall follow the informed consent process set forth in Section 5.2 and obtain the signature and date from the patient on the approved Patient Informed Consent (PIC) form (previously approved by Ethics Committee and the Sponsor). If the patient does not sign and date the Patient Informed Consent (PIC), they cannot participate in the investigation. No further CIP required activities are allowed.

A patient becomes a subject once he/she has been fully informed about the investigation, has agreed to participate, signed & dated the PIC and therefore has been enrolled in the investigation.

NOTE: As soon as the subject signs the Patient Informed Consent, adverse events need to be reported according to the guidelines mentioned in Section 5.3.

The EC should be notified appropriately about any CIP deviations with regards to obtaining informed consent.

If new information becomes available during the clinical study that can significantly affect a patient's future health and medical care, that information will be provided to the patient(s) in written form.

The following information will be collected at the baseline visit either from hospital records or through patient interaction documented in the hospital records. All baseline activities are performed after the patient is enrolled in the investigation. Tests and procedures required at baseline can be completed within 90 days of enrollment but must be completed prior to procedure.

4.1.1 Medical History

A complete medical history of the subject will be reviewed and recorded including:

- Hypertension, renal, cardiovascular, neurological, obstructive sleep apnea, hyperlipidemia, diabetes (Type I and II), smoking, thyroid disease, liver disease, chronic obstructive pulmonary disease, and alcohol consumption

4.1.2 Physical Assessment

The subject will have a physical assessment recording at the baseline visit to capture the following:

- Age
- Gender
- Height (only at baseline)
- Weight

4.1.3 Office Blood Pressure

Office Blood Pressure measurements will be recorded as the average Blood Pressure of three measurements. If there is a change in medication after the office Blood Pressure assessment is completed an additional set of office Blood Pressure measurements is required to determine eligibility.

Measurements should be taken according to Standard Joint National Committee VII Guidelines / ESC and ESH Guidelines[54, 55], refer to Appendix A for Office Blood Pressure instructions.

4.2 Two Week Screening Period

4.2.1 Medication Regimen Monitoring (≥14-Day Period)

The anti-hypertensive drug regimen of the subject will be monitored for a period of at least 14 days at baseline. Medication logs will be provided for the subject to record their daily anti-hypertensive drug regimen during the monitoring period. Upon the completion of the monitoring period (≥14 days), the subject will return to the study center with the medication logs for the continued baseline evaluation.

The medication log will be reviewed to assess the subject's compliance with their current medication regimen. The clinical investigation does allow the inclusion of subjects that are not on guideline based therapy due to intolerance. Intolerance to medications is defined as a relative or an absolute contraindication to an anti-hypertensive medication. This assessment will be left to the discretion of the Study Investigator.

It is recommended that the subjects maintain their enrollment anti-hypertensive regimen for a minimum of 180 days post procedure unless clinically necessary for changes to occur.

Investigators will urge subject compliance to prescribed medical regimen at the onset of the 14 day monitoring period and throughout the trial. If the subject is non-compliant without medical rationale, the subject may be excluded.

4.2.2 Ambulatory Blood Pressure

To ensure proper patient selection for inclusion in the study subjects must have a daytime mean Ambulatory Blood Pressure (ABP) measurement of > 135 mmHg within 90 days prior to procedure.

If there is a change in medication after ABP assessment an additional ABP assessment is required to determine eligibility. In addition to the daytime mean ABP, the night time mean, and 24 hour average ABP value will be collected. When using ABP ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00) and 1 measurement per hour are taken during the person's usual night time hours. The average value of at least 14 measurements taken during the person's usual waking hours should be used for calculation of mean daytime value.

Measurements should be taken according to Standard Joint National Committee VII Guidelines ESC and ESH Guidelines54, 55, refer to Appendix B for 24 Hour Ambulatory Blood Pressure instructions.

The ABP can be taken during the two week screening period but must be repeated if there are medication changes. .

4.3 Confirmatory Visit

After the two week screening period the subject will return to the Study Center for the confirmatory visit.

The following items will be reviewed or performed at the confirmatory visit to ensure there have been no changes prior to moving forward with the EnligHTN Renal Denervation procedure.

- Inclusion / exclusion criteria
- Medication logs
- Medical history & physical assessment
- Office Blood Pressure measurements will be recorded as the average Blood Pressure of three measurements
- Review of daytime mean Systolic Ambulatory Blood Pressure (must be repeated if there are medication changes)

If the subject does not meet eligibility after baseline and 2 week screening period they may be re-evaluated. The Office Blood Pressure, Medication log and the Ambulatory Blood Pressure will need to be repeated if it is determined the subject could be re-evaluated.

4.3.1 Blood and Urine Analysis

Blood and urine samples will be collected and analyzed as listed below.

- Serum Creatinine
- Estimated GFR (eGFR)

- Hemoglobin A1c
- Fasting glucose
- Fasting insulin
- Urine albumin-creatinine ratio
- Pregnancy test (only at baseline)

A true numeric value for the estimated GFR must be provided. If your local laboratory does not report the eGFR value beyond 60 mL/min/1.73 m^2 the center should use a sponsor-approved calculation tool to generate the value. The sponsor will provide an approved website(s) for this calculation to study centers.

4.3.2 Transthoracic-echocardiogram (TTE)

Transthoracic-echocardiogram (TTE) examinations will be conducted at approximately 6 sites. Each site is responsible for performing the echocardiogram per each institutions standard of care echo protocol.

4.3.3 NYHA Assessment

NYHA Assessment[57] will be evaluated at baseline and should be classified based on the definitions in Appendix C.

4.3.4 Quality of Life Questionnaire

EQ-5D 5L questionnaire will be completed at baseline.

4.3.5 Baseline Renal Artery Anatomy Evaluation

Adequate renal artery imaging is recommended to occur within 90 days prior to enrollment. Renal artery imaging by Duplex Ultrasound (U/S) should be performed to evaluate the subject's renal artery anatomy. Study investigators may consider requesting a computed axial tomography scan (CT scan) or utilize the procedural angiogram if the Duplex Ultrasound is inconclusive or shows any renal abnormalities.

Renal artery evaluation data collected will include but are not limited to:

- Type of evaluation - computed axial tomography (CT scan), duplex ultrasonography, angiography, Doppler, magnetic resonance (MR) angiography, or non-contrast MRI
- Length of artery(s)
- Diameter of artery(s)
- Number of main renal arteries
- Number of accessory renal arteries
- Presence and percent of stenosis
- Other abnormalities

4.4 Subject Group Assignment

Subjects who have met all of the baseline and enrollment criteria will be assigned to one of the following groups:

4.4.1 Group A: (minimum of 100 subjects)

- Office systolic Blood Pressure ≥160 mmHg
- Subject is taking ≥3 anti-hypertensive medications (including 1 diuretic), or subject has documented drug intolerance to 2 or more of the 4 major classes of anti-hypertensives (ACE/ARB, Calcium Channel Blockers, Beta Blockers, or diuretic) and is unable to take 3 anti-hypertensive drugs.
- Patient has an estimated GFR ≥45 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula

4.4.2 Group B: (minimum of 50 subjects)

- Office systolic Blood Pressure ≥140 mmHg
- Subject is taking ≥3 anti-hypertensive medications (including 1 diuretic), or subject has documented drug intolerance to 2 or more of the 4 major classes of anti-hypertensives (ACE/ARB, Calcium Channel Blockers, Beta Blockers, or diuretic) and is unable to take 3 anti-hypertensive drugs.
- Patient has an estimated GFR ≥45 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula

4.4.3 Group C: (minimum of 50 subjects)

- Office systolic Blood Pressure ≥140 mmHg
- Subject is taking ≥3 anti-hypertensive medications (including 1 diuretic), or subject has documented drug intolerance to 2 or more of the 4 major classes of anti-hypertensives (ACE/ARB, Calcium Channel Blockers, Beta Blockers, or diuretic) and is unable to take 3 anti-hypertensive drugs.
- Patient has an estimated ≥15 GFR <45 mL/min per 1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) formula

4.5 Renal Denervation Procedure

The renal nerve ablation should be performed according to the EnligHTN™ Renal Denervation System Instructions for Use (IFU).

The renal denervation procedure should always be done with the aid of fluoroscopy. With the patient under local anesthesia, an introducer sheath will be inserted into the femoral artery using the standard percutaneous technique (modified Seldinger technique). A heparin bolus of 3000 to 5000 units will then be administered intravenously or per institution's standard of care. An 8 French guiding catheter sheath will be inserted to engage each main renal artery sequentially with the angiograms recorded. Images of the left and right main renal arteries will be recorded using the non-ionic contrast and the diameter and length of each of the main renal arteries will be measured.

Prepare the patient for standard electrosurgery. Select an appropriate basket size of the Basket Renal Denervation Catheter (small size for patient with renal artery diameter between 4mm and 6mm and large size for patient with renal artery diameter between 5.5mm and 8mm) should be chosen. The Basket Renal Denervation Catheter will be inserted with the tip of the catheter positioned proximal to the bifurcation of one of the main renal arteries and the corresponding images will be recorded. The basket on the Renal Denervation Catheter will then be opened, while the impedance of each electrode on the basket will be monitored. To begin the ablation, the "START" button on the RF Generator will be pressed with the impedance, temperature and RF energy delivery monitored and recorded during the process. The investigator will decide the location(s) and number of ablation sites/lesions (4 to 8 ablation sites/lesions are recommended) in the main renal artery. When the ablation procedure is completed in this main renal artery, the basket on the Catheter will be withdrawn from the artery with the Basket Renal Denervation Catheter fully closed. Images of the renal artery using the non-ionic contrast will be recorded. Any signs of renal artery irregularities (vasospasm, stenosis or dissection) will be checked.

The same renal artery ablation procedure will be repeated for the other main renal arteries. When the ablation procedure for the main renal arteries are also completed, the basket on the Renal Denervation Catheter will be withdrawn from the artery with the Basket Renal Denervation Catheter fully closed and the catheter will be visually inspected and flushed with heparinized saline. Finally, the sheath will be removed according to the center's standard of care.

Procedural data collected will include but is not limited to:

- EnligHTN™ Renal Denervation System device information
- Guiding catheter used – manufacture
- Number of arteries ablated
- Number of ablations performed
- Device settings
- Procedure time
- Ablation time
- Fluoroscopic time
- Volume of contrast media

4.6 Product Training

All physician users will undergo product training prior to initial human use and at the time of initial human use there is an expectation that each site will be proctored by a SJM clinical specialist until there is demonstration of product usage per the IFU and site ancillary procedural staff have been trained on the ablation generator.

4.7 Discharge

Following the renal denervation procedure, the subject's blood pressure will be monitored every 4 hours post procedure until discharge, or for a maximum of 24 hours. At discharge a physical assessment will be performed and the subject's medication regimen will be reviewed and recorded. Discharge is expected to occur within72 hours post procedure.

Adverse Events – check if any adverse events or adverse device effect occurred since enrollment of the patient into the Clinical Investigational study. Document the event in the hospital records and report the adverse event according to specifications in section 5.3.2.

4.8 Follow-up visits

Subjects will return for follow-up at 1 month (±14 days), 6 months (± 30 days) post procedure and annual follow-up visits at 12, 24, 36, 48, and 60 months post-procedure (± 60 days).

The following will be evaluated / reviewed according to Table 1:

4.8.1 Physical Assessment

The subject will have a physical assessment at every follow up visit to capture weight.

4.8.2 Medications

Medications will be recorded in addition to documenting changes to medications at each follow-up visit.

4.8.3 Office Blood Pressure

Office Blood Pressure measurements will be recorded as the average blood pressure of three measurements at each follow-up visit. Measurements should be taken according to Standard Joint National Committee VII Guidelines / ESC and ESH Guidelines 54, 55 (Refer to Appendix A for Office Blood Pressure instructions).

4.8.4 24 hour Ambulatory Blood Pressure

24 hour Ambulatory Blood Pressure measurements should be taken according to Standard Joint National Committee VII Guidelines / ESC and ESH Guidelines [54, 55](Refer to Appendix B for 24 Hour Ambulatory Blood Pressure instructions) at each follow-up visit.

In addition to the daytime mean ABP, the night time mean, and 24 hour average ABP value will be collected. When using ABP ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00) and 1 measurement per hour are taken during the person's usual night time hours. The average value of at least 14 measurements taken during the person's usual waking hours should be used for calculation of mean daytime value.

4.8.5 Blood and Urine Analysis

Blood and urine samples will be collected and analyzed as listed below.

- Serum Creatinine – to be collected at 6M, 12M, 24M, and 60M follow-up visit.
- Estimated GFR (eGFR) – to be collected at 6M, 12M, 24M, and 60M follow-up visit.
- Hemoglobin A1c – to be collected at the 6M follow-up visit only
- Fasting glucose – to be collected at the 6M follow-up visit only
- Fasting insulin – to be collected at the 6M follow-up visit only
- Urine albumin to creatinine ratio – to be collected at the 6M, 24M, and 60M follow-up visit.

A true numeric value for the estimated GFR must be provided. If your local laboratory does not report the eGFR value beyond 60 mL/min/1.73 m^2 the center should use a sponsor-approved calculation tool to generate the value. The sponsor will provide an approved website(s) for this calculation to study centers.

4.8.6 Echocardiogram (TTE)

Transthoracic-echocardiogram (TTE) examinations will be conducted at approximately 6 sites at the 1M, 6M, 24M, and 60M follow-up visit. Each site is responsible for performing the 3D echocardiogram per each institutions standard of care echo protocol.

4.8.7 NYHA Assessment

NYHA Assessment[57] will be evaluated at the 1M, 6M, 24M, and 60M follow-up visit and should be classified based on the definitions in Appendix C.

4.8.8 EQ-5D 5L Quality of Life Questionnaire

EQ-5D 5L questionnaire will be completed at 1M, 6M, 24M, and 60 M follow-up visit.

4.8.9 Renal artery evaluation

Renal artery evaluation will be completed at the 6M, 24M, and 60M follow-up visit. Duplex Ultrasound (U/S) is the recommended imagine modality, however this evaluation can be completed by either: computed axial tomography (CT scan), duplex ultrasonography, Doppler,

angiography, magnetic resonance (MR) angiography or non contrast magnetic resonance imaging.

If a renal artery evaluation is completed at any other time point this data will also be collected during the study.

4.8.10 Adverse Events

Confirm if any adverse events or adverse device effect occurred since the last visit and document in the hospital records. Report the adverse event according to specifications in section 5.3.2.

4.9 Clinical Investigation Termination

Each subject will be followed for 5 years post renal denervation procedure or until time of death, loss of follow up, withdrawal or clinical investigation termination. The clinical investigation will be complete after all follow-up visits are performed, all data is received by the Sponsor and the database is locked. The study will be closed when a final report is written on the conclusions and analysis of the data.

Participation in this clinical investigation is voluntary. Subjects are free to withdraw from the clinical investigation at any time without reason. Should this occur, the reason for discontinuation must be recorded in the source documents. However, subjects should be strongly encouraged to complete the CIP required follow up. Should a subject wish to withdraw prior to completing 60 month follow-up, the investigator should request the subject to come in for a final visit and a Clinical investigation Termination CRF should be completed by the site and provided to the Sponsor.

At this visit the subject will undergo the following evaluations:

- Office Blood pressure measurement
- Blood/Urine labs

In a situation where a clinical investigation withdrawal is due to an adverse event the subject should be followed until resolution of that adverse event or determination that the subject's condition is stable.

Subjects must be informed about their right to withdraw from the investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the investigation will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the investigation at any time. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the investigation. All reasonable efforts should be made to retain the subject in the clinical investigation until completion of the investigation.

Other reasons for termination or withdrawal include, but are not limited to, the following:

- Subject did not meet the inclusion/exclusion criteria

- Subject death (in case of subject death, cause must be documented)
- Subject and/or family request
- Subject non-compliance
- Subject lost to follow-up, defined as the following: a subject will be considered "lost to follow-up" after a minimum of 2 documented phone calls of a physician or delegate at the study site to the subject or emergency contact and a certified letter sent to the last known address
- Subject's participation terminated by Investigator
- Study terminated by SJM
- The study terminated according to locally applicable regulations
- The study may be temporarily stopped or terminated, either at the local, national, or international level, at the request of Ethics Committees, regulatory authorities, or SJM.

4.10 Description of post investigational provision of medical care

When the subject's participation in the clinical investigation has been completed (prematurely) or terminated, the subject will return to the medical care as per physician's recommendation.

5 Clinical Investigation Conduct

5.1 Ethics Committee

A duly constituted EC representing the prospective study site must review and approve the subject informed consent and research authorization document, the study protocol, the prospective investigator's participation in the study, and any other study related information to be provided to the subjects prior to subject enrollment. Additionally, the Investigator must be aware of and adhere to all EC requirements such as, but not limited to: the submission of progress reports, serious adverse events, and protocol deviations.

EC approval record should clearly identify:

- the date of the meeting
- constitution of the committee and voting members present at the meeting
- the approved version of the Clinical Investigation Plan
- the approved version of the Patient Information Sheet and subject Informed Consent
- the approved version of the Investigator's Brochure
- the approved version of the Instructions for Use (IFU)

Approval from the EC is necessary prior to the start of the investigation. The original approval is to be filed in the Investigator Study Binder and a copy of the approval is provided to SJM prior to the first investigational assessment.

Any amendments to the protocol should be submitted to the relevant EC. The EC will be informed about SAEs and UADEs in accordance with local and national requirements.

Prior to SJM receiving data from the study site, the study protocol will be reviewed and approval obtained from the study site EC. There are no additional Board reviews for the study.

5.2 Ethical Basis

This clinical investigation will be performed in accordance with the World Medical Association Declaration of Helsinki (Appendix F) and applicable local and national legal and regulatory requirements. Prior to starting the investigation, the Clinical Investigation Plan will be submitted together with associated documents including Patient Information Sheets, and subject Informed Consent Forms in the local language to the relevant EC for review.

5.3 Insurance

St. Jude Medical, as the Sponsor, has taken out insurance for all subjects participating in this study in accordance with the requirements of the local laws.

5.4 Statements of Compliance

The investigation will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki and any regional and/or national regulations, as appropriate.

The investigator shall not start enrolling subjects or requesting informed consent prior to obtaining Ethics Committee approval and authorization from the sponsor in writing for the investigation.

In case additional requirements are imposed by the Ethics Committee, they shall be followed, if appropriate.

As sponsor, SJM will maintain insurance for this investigation in accordance with the requirements of the applicable local laws.

5.5 Adherence to the Clinical Investigation Plan

The Principal Investigator and delegates are required to adhere to the CIP in order to prevent subjects being exposed to unreasonable risks. The Principal Investigator and delegates are also required to be compliant with the signed Study Agreement, applicable national or local laws and regulations, and any conditions required by the appropriate EC or applicable regulatory authorities are expected as well. Instances of failure, intentionally or unintentionally, to adhere to the requirements of the CIP are considered a deviation and corrective action(s) may be taken to prevent these instances from occurring again.

In some cases failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the Sponsor to exclude subjects for whom the device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety

and well-being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well-being of the enrolled subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks. It is the responsibility of the investigator to provide adequate medical care to a subject enrolled in an investigation.

The PI shall promptly report any deviations from the CIP to the Sponsor that affects the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances. The reporting of these deviations should be done as soon as possible but no later than 72 hours after the investigator becomes aware. The investigator shall also promptly notify the EC, as per their requirements.

Any corrective and preventive actions required by the EC must be complied with by the site.

The Sponsor will notify the EC as per their requirements.

5.5.1 Repeated non-compliance

In the event of repeated non-compliance, as determined by the Sponsor, a Clinical Research Associate or sponsor representative will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing
- Retraining of the investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical investigation, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical investigation.

5.6 Informed Consent Process

5.6.1 General Process

Provision of the Informed Consent is mandatory. Informed Consent is required from all patients prior to participation in the investigation. The process of obtaining Informed Consent shall comply with the most recent version of the Declaration of Helsinki, ISO 14155:2011 and all applicable regulations.

The Principal Investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate in the clinical investigation. It is crucial that this discussion is documented in the source documents (hospital records).

Prior to enrolling in the clinical study, patients shall be fully informed of the details of clinical study participation as required by applicable regulations and the study center's EC, and/or Head of Medical Institution. Informed consent must be obtained from each patient prior to any clinical study participation using the Patient Information Sheet (PIS) and Patient Informed Consent form (PIC) approved by both the Sponsor as well as that study center's EC, and/or Head of Medical Institution. Prior to the patient signing the PIS, the investigator or authorized delegate will fully explain to the patient the nature of the research, clinical study procedures, anticipated benefits, and potential risks of participation in the clinical study.

The patient will be provided with the EC approved patient information sheet and informed consent form that is written in a language that is understandable to them (native non technical language) and sufficient time is provided to the patient to consider participation and ask questions if necessary. The study site personnel will provide answers to the patient's questions.

If a patient is unable to read or write, the consenting shall be obtained through a supervised oral process. An independent witness shall be present throughout the process. The consent form must be signed and dated by the patient and by the person obtaining the consent attesting that the information was accurately explained and that informed consent was freely given.

The consent form must be signed and dated by the patient and by the person obtaining the consent.

If the patient does not sign and date the PIC, they cannot participate in the investigation. No further CIP required activities are allowed. If the patient has provided written informed consent, obtain signature and date from the Principal Investigator or authorized designee on the EC approved informed consent form.

In order to avoid any possible coercion or undue improper influence on, or inducement of the patient to participate, the Sponsor requests the investigator to only sign the informed consent form once the subject has signed and dated the document and therefore decided to participate in the investigation.

Informed Consent of a subject shall always be indicated by personally dated signature of the subject and by the investigator responsible for conducting the Informed Consent process.

The original signed consent document must be retained on file by the investigator and a copy of the signed consent document is provided to the subject (investigator's responsibility).

The subject's legal rights will not be waived, nor will it appear that these will be waived.

Important new information that becomes available throughout the clinical investigation will have to be provided in writing to new and existing subjects. If relevant, all affected subjects will be provided a new consent form to review and re-sign, should they decide to maintain participation in the investigation.

5.7 Adverse Event, Adverse Device Effect

Definitions

The definitions provided below are in accordance to ISO 14155:2011 (E).

5.7.1 Medical device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article.

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
    - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
    - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
    - Investigation, replacement, modification, or support of the anatomy or of a physiological process,
    - Supporting or sustaining life,
    - Control of conception,
    - Disinfection of medical devices and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

5.7.2 Adverse Event (AE)

Any 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 medical device.

Note: This definition includes events related to the medical device or the comparator.
Note: This definition includes events related to the procedures involved.

5.7.3 Serious Adverse Event (SAE)

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
    - A life-threatening illness or injury OR
    - A permanent impairment to a body structure or a body function OR
    - An in-patient or prolonged hospitalization OR
    - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
    - A malignant tumor
- Fetal distress, fetal death or a congenital abnormality or birth defect

Note: A 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.

5.7.4 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational device.

Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

Note: This definition includes any event resulting from the use error or from intentional misuse of the medical device.

5.7.5 Serious Adverse Device Effect (SADE)

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

5.7.6 Unanticipated Serious Adverse Device Effect (USADE)

A 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.

5.7.7 Anticipated Serious Adverse Device Effect (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

5.7.8 Procedure for assessing, recording and reporting adverse events, adverse device effects, serious adverse events and serious adverse device effects*:*

Safety surveillance and reporting will be done for all subjects enrolled in this investigation as described below.

Safety surveillance within this investigation and the safety reporting performed by the investigator, starts as soon as the subject is enrolled in this investigation (date of signature of the informed consent). The safety surveillance and the safety reporting will continue until the last investigational visit has been performed or the subject is deceased or the subject/investigator concludes his participation into the investigation.

For the purpose of this trial, all Serious Events (regardless of relatedness) and all Adverse Device Effects (regardless of severity) will be reported via an eCRF to the sponsor. All Serious Adverse Events and all Adverse Device Effects (serious or non-serious) are to be documented and reported by the investigator to the sponsor immediately but no later than 72 hours after becoming aware of the event.

Adverse events will be assessed by the investigator for relationship to the device and to the procedures involved.

- Procedure related: The AE is deemed related to the procedure if it occurred during the procedure but was not directly caused by the medical device.
- Device related: The AE is deemed device related if it was directly caused by the medical device.

Investigators are responsible for promptly reporting all SAEs and ADEs to the sponsor by completing the Adverse Event form. All unresolved AEs should be followed by the investigator until resolution is reached.

Note: Refer to Table 1 'Data Collection' and Appendix G 'Data Collection Method'.
In case of EDC failure, notify Sponsor via Fax or via *E2AdverseEvent@sjm.com*.

5.8 Subject Death

5.8.1 Procedure for recording and reporting Subject Death

The investigator will document and report all subject deaths to the sponsor immediately but no later than 72 hours after becoming aware of the event.

Should death occur, the investigator should record the information in the hospital records and immediately document the information on the Death Form. By completing the form the sponsor will be notified.

Note: Refer to Table 1 'Data Collection' and Appendix G 'Data Collection Method'
In case of EDC failure, notify Sponsor via Fax or via *E2AdverseEvent@sjm.com*.

Subject Death is an outcome of a serious adverse event (SAE). Death is therefore related to an SAE and all efforts to obtain the SAE details should be made and the Adverse Event form must be completed. Any supporting documentation (autopsy records, death certificates, hospitalization records) must be sent to SJM with the corresponding SAE and Death CRFs.

The subject's death is an Early Conclusion of the subject's participation in the investigation. Therefore, the investigator is requested to complete the Termination form.

The investigator must notify the EC, if appropriate, in accordance with national and local laws and regulations.

5.9 Document and data control

5.9.1 Traceability of documents and data

The investigator shall ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the electronic case report forms (eCRFs) and in all required reports. When copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

5.9.2 Recording data

Source documents shall be created and maintained by the investigational site team throughout the clinical investigation.

The data reported on the eCRFs shall be derived from, and be consistent with, source documents, and any discrepancies shall be explained in writing.

The eCRFs shall be validated by the Principal Investigator or a delegated investigator. Any change or correction to data reported shall be dated and explained if necessary. The original entry will remain available by audit trail.

5.9.3 Review of data

The clinical investigation will be monitored by reviewing the eCRF approved by the investigators.

The following activities will occur:

- All eCRFs will be reviewed for completeness and accuracy after being uploaded into the database.
- The investigator (co-investigator) and/or delegate is notified regarding any missing or unclear/inconsistent data.

5.10 Monitoring

On site-monitoring shall be performed during the clinical investigation in order to guarantee adherence to all applicable regulations, the Clinical Investigation Plan and the signed Clinical Study Agreement. By monitoring, the Sponsor can also verify the accuracy of data collected on the accompanying eCRFs throughout the duration of the clinical investigation.

Monitoring is necessary to ensure adequate protection of the rights and safety of human subjects involved in the clinical investigation and the quality and integrity of the data obtained during the investigation. The sponsor will at the same time assess the investigational site and study team on staffing and facilities to ensure the investigation can continue in a safe and effective fashion.

During the monitoring visits, data reported on the eCRF shall be reviewed as specified in the monitoring plan.

5.10.1 Designated Monitors

Only monitors qualified by education, training and experience, which have been trained on the Clinical Investigation Plan, eCRF content, Monitoring Plan, relevant requirements and informed consent process will be allowed to perform monitoring activities during this clinical investigation. The monitor's qualifications and training will be documented by the sponsor. A list of monitors is available upon request.

5.10.2 Monitoring Plan

Prior to the start of the site monitoring activities for this clinical investigation, a project specific Monitoring Plan (MP) will be created.

At a minimum, the Monitoring Plan will include the following:

- Required activities
- Frequency of monitoring visits
- Visit Requirements
- Procedures for securing site compliance
- Monitoring report content and timelines
- Close-out procedures

The Monitoring Plan may be updated as appropriate. All revisions will be tracked.

5.11 Competent Authority (CA) Inspections

The investigator and/or delegate should contact SJM immediately upon notification of a CA inspection at the site. A clinical monitor will assist the investigator and/or delegate in preparing for the inspection.

An investigator who has authority to grant access shall permit authorized CA employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the investigation, shall permit authorized CA employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the investigation.

An investigator shall permit authorized CA employees to inspect and copy records that identify subjects, upon notice that CA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or EC have not been submitted or are incomplete, inaccurate, false or misleading.

5.12 Investigation Termination

The Sponsor reserves the right to suspend or terminate the investigation in an individual site or the entire clinical investigation for significant and documented reasons, at any stage, with appropriate written notice to the investigator.

The investigation will be terminated according to applicable regulations.

The investigator shall return all documents to the sponsor; and notify the Ethics Committee and the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per standard of care.

5.12.1 Resuming the Clinical Investigation after Suspension

The sponsor shall conclude an analysis of the reason(s) for the suspension, implement the necessary corrective actions, and decide to lift the temporary suspension. The sponsor shall inform the Principal Investigators, EC/Head of Medical Institution or regulatory authority, where

appropriate, and the regulatory authority of the rationale, providing them with the relevant data supporting this decision.

Concurrence shall be obtained from the, EC/Head of Medical Institution or regulatory authority where appropriate, before the clinical investigation resumes.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee shall inform them of the reasons for resumption.

5.12.2 Investigation Conclusion

The investigation will be concluded at an individual study site when:

- A Close Out visit has been performed by the Sponsor AND
- The Final report has been provided
- The final report/close-out is acknowledged by the study site's EC

6 Risks and Benefits of the Clinical Investigation

6.1 Anticipated Adverse Events and Adverse Device Effects

Possible adverse events associated with the renal denervation procedure include, but are not limited to:

- Acute renal injury (renal infarction, renal hematoma)
- Renal vascular injury (renal artery dissection, renal artery thrombosis, renal artery stenosis)
- Collateral tissue injury
- Malignant or accelerated hypertension
- Symptomatic hypotension
- Access site complications (arteriovenous fistula, access site thrombosis, embolisation, pseudo-aneurysm, hematoma, limb ischemia, femoral nerve injury, or seroma)
- Disseminated intravascular coagulation
- Infection (access site infection or systemic infection)
- Renal failure
- Decompensated heart failure
- Myocardial infarction
- Neurologic event (acute ischemic or hemorrhagic brain injury)
- Respiratory compromise
- Pain, including Back Pain
- Death
- Drug reactions
- Contrast allergies etc
- Bradycardia
- Vasospasms
- Vasovagal episodes

6.2 Steps that will be taken to control or mitigate the risks

Every possible effort will be taken to minimize the risks, including:

- Careful selection of experienced investigators for the clinical investigation
- Regular clinical investigation monitoring visits for each clinical investigation center
- Conduction of the clinical investigation in accordance with the Clinical Investigational Plan (CIP), all applicable laws and regulations (e.g. ISO14155:2011) and any conditions of approval imposed by the appropriate EC or applicable regulatory authorities where the clinical investigation is performed
- Preparation of the catheter and performance of the renal denervation procedure in accordance with the device IFUs.
- Catheter advancement under fluoroscopic imaging to minimize the risk of arterial damage.
- Training of Investigators both on the CIP and EnligHTN Renal Denervation procedure

7 Statistical Analysis

7.1 Study design

This is a post market, prospective, international, multicenter, non-randomized, single arm study of the EnligHTN™ Renal Denervation System. Approximately 500 subjects with uncontrolled hypertension will undergo renal artery ablation at approximately 40 investigational sites located internationally and will be followed up to five (5) years post procedure. Subjects will be included in one of three groups: Group A, Group B and Group C (Refer to Section 4.1 for detailed criteria for each group).

The primary objective is to evaluate a mean reduction of office Systolic Blood Pressure at six (6) months post renal denervation.

7.2 Sample size estimation

The sample size of approximately 500 patients is used considering the study objectives; to observe the proportion of patients with a mean reduction of systolic blood pressure at 6 months, and peri-procedural events within 30 days post procedure. Approximately 40 Investigational sites will be invited to participate. A sample size of 500 patients will allow for each site to contribute a reasonable number of patients for this multicenter study. No formal power analysis or hypothesis test will be performed. However the data collected will be analyzed and presented using the descriptive or appropriate summary statistics.

7.3 Analysis Population

All patients who have signed a Patient Informed Consent (PIC) will be considered enrolled in the study. However, Primary Analysis population will include those patients that have signed a PIC, and had the EnligHTN™ Renal Denervation System enter his/her body. The sample size of 500 are those subjects in the Primary Analysis population.

As Treated population will include all subjects in whom renal denervation was performed in a minimum of one renal artery per kidney (according to the Instructions for Use).

It is anticipated that there may be subjects who have enrolled in the study but are not included in the Primary Analysis population or As Treated population, such as:

- Subjects who are enrolled but do not meet baseline inclusion or exclusion criteria before the procedure; these are considered the screen failure population.
- Procedurally excluded populations will include subjects who have enrolled in the study and start the procedure, but do not have the EnligHTN™ Renal Denervation System enter his/her body, due to their anatomy, circumstances related to the procedure, or physician judgment.

Subjects that withdraw from the investigation will not be replaced in any analysis population.

7.4 Data Analysis and Reporting

In general data analysis will be performed across all subjects, as well as within each of three groups (Group A, B and C), based on Primary Analysis population unless otherwise specified.

The data collected will be presented using the appropriate summary statistics. Continuous data will be summarized using descriptive statistics (mean, number of observations, standard deviation, minimum and/or maximum values) and categorical data will be summarized using frequencies and percentages.

7.4.1 Primary objective

The mean reduction of office SBP at six (6) months of the study will be analyzed by:

1. Computing the reduction of SBP measurements at 6 months compared to baseline for each patient with data available in both time points.

2. Calculating the mean and standard deviation of the SBP reduction at 6 months

7.4.2 The Secondary objectives

7.4.2.1 Safety Acute data (30 days post procedure)

- The peri-procedural events within 30 days post procedure will be summarized as percentage of patients defined as:

$$\frac{Number\ of\ subjects\ with\ \text{peri procedural events within 30 days post procedure}}{Number\ of\ subjects\ at\ baseline\ for\ that\ population} * 100$$

7.4.2.2 Safety Midterm (6 months) and Long term (2 and 5 years) data

- The new renal artery stenosis (>50%) and/or aneurysm at the site of ablation per Renal Artery Imaging (CT/MR) will be summarized at 6 months, 2 and 5 years as percentage of patients who have stenosis and/or aneurysm. Kaplan-meier analysis may be performed on the time to the first new renal artery stenosis and/or aneurysm at the site of ablation, as appropriate.
- Renal function change based on eGFR will be summarized by:

  1. Computing the change of the eGFR at 6 months, 2 years and 5 years compared to baseline for each patient with data available in both time points.

  2. Calculating the mean and standard deviation of the eGFR change at those interval

7.4.2.3 BP reduction

The data of

- Change in Ambulatory Blood Pressure parameters at 6 months,
- Change in Office Diastolic Blood Pressure at 6 months,
- Change in Office and Ambulatory Blood Pressure parameters

at 12, 24, 36, 48, 60 months post denervation will be calculated in the same way as described in the calculation of SBP reduction at 6 month (Section 7.4.1)

- The percentage of subjects achieving office SBP < 140 at 6 months visit will be computed as follows:

$$\frac{Number\ of\ subjects\ achieving\ office\ SBP\ <\ 140\ at\ 6\ months\ visit}{Number\ of\ subjects\ \ with\ \ data\ available\ in\ 6\ months\ visit} * 100$$

7.4.3 Other Analyses

In addition, subgroup analyses may be performed as needed such as for subjects that have the renal denervation procedure performed on one side but not the other, due to their anatomy, circumstances related to the procedure, or physician judgment; and by the patient's primary disease states/conditions.

Ad Hoc analyses may be performed as needed. Analysis may be performed based on As Treated population as appropriated. In general, data analysis will be performed on a per subject basis. But the data analysis may be presented per kidney, or on renal artery basis, as appropriate.

7.4.4 Analysis Software

The statistical analyses will be performed using SAS™ software version 9.2, or as specified and appropriate.

8 Data Management

All documents and data shall be produced and maintained in a way that assures control and traceability. Where relevant, the accuracy of translations shall be guaranteed and documented. All documents, and subsequent versions, related to a clinical investigation shall be identifiable, traceable and appropriately stored to provide a complete history of the clinical investigation.

eCRFs shall be developed by Sponsor to capture the data for each enrolled subject as required by the CIP. The eCRFs shall include information on the condition of each subject upon entering, and during the course of the clinical investigation, exposure to the device and any other therapies.

The Sponsor will be responsible for the data handling.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations worldwide and/or any other worldwide regulatory authorities in support of a market-approval application.

8.1 Data Management Plan

eCRF data will be entered by authorized investigative site personnel in a validated electronic database.

The Data Validation Procedure (DVP), will be part of the Data Management Plan (DMP), and describes all the computerized data cleaning checks (validation rules) as programmed at the time of database set-up. These validation rules may change and be updated throughout the course of the investigation.

Manual review and Data Cleaning Convention (DCC) will be used in addition to computerized data cleaning checks, to check for discrepancies and to ensure consistency of the data.

All revisions of the DMP will be tracked and include an effective date.

8.2 Source Documents

Source documents shall be maintained by the investigation site team throughout the clinical study. All findings in this clinical study must be documented as source data, and therefore can be verified (and audited). Source documentation may be paper or electronic, and is defined as the first time the data appears and may include for example; all clinical records, hospital records, surgery reports, autopsy reports, and any other material that contains original information used for clinical study data collection or adverse event reporting.

8.3 Source Data and Subject Files

The investigator shall keep written or electronic subject files for every subject participating in the clinical investigation. In this file, the available demographic and medical information of a subject shall be documented, in particular the following:

Name	Age	Weight
Gender	Height	Concomitant Medication
Subject History	Concomitant diseases	Scheduled follow ups
PIC process	Date of PIC	Observed AEs
CIP required examination	Clinical findings	Procedure Notes

It should be possible to verify the inclusion and exclusion criteria for the investigation from the available data in this file. It must be possible to identify each subject by using this subject file. Additionally, any other documents with source data have to bear at least the subject identification and the printing date printed by the recording device to indicate to which subject and to which procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator. All data recorded on the eCRF must also be part of the subject's source data.

8.4 Confidentiality of Data

All subject information collected during the course of this study will be kept strictly confidential according to applicable country-specific laws and regulations. All data and information concerning subjects and their participation in this study are considered confidential by St. Jude Medical, Cardiology Division, Inc., d/b/a St. Jude Medical, Cardiovascular Division, Inc., a U.S. company, and its affiliates (located in the U.S.A. and European Economic Area (EEA), Canada, and other countries), and other people who work for SJM to provide services related to the device and this study (collectively referred to as "SJM"). All public reporting of the results of the study will eliminate identifiable references to the subjects. Information on paper will be kept in secured locations. Electronic information will be kept on password-protected computers.

Personal data, including medical and health information, will be processed both by computer and manually, during and after the study by SJM, and its affiliates, its designated third party data processors, the EC, the institution conducting the study, the study doctors and other healthcare personnel involved in the study for the purposes of this study. The electronic data stored for this study will be kept in an SJM database, in compliance with applicable law. Subject data will not contain details of study subject identity. The data will be stored on a secure server and backed up routinely. Personal data will be key-coded to prevent subject identification, except by the institution, study doctors and other healthcare personnel involved in the study, if necessary for the purpose of the study, for regulatory inspections, and to comply with SJM reporting obligations.

Study subjects have a right to gain access and to correct inaccuracies in information about them as permitted by applicable law.

In order to help keep subject medical records and personal information confidential only certain authorized investigators and SJM personnel, or approved contracted agents of SJM, will have access to confidential records. These include researchers in the hospital who are part of this study, SJM and its affiliates and representatives that perform study-related services who may be located in the U.S.A., Canada, European Economic Area (EEA) and other countries. The Ethics Committee (EC) and other regulatory authorities also have the right to inspect and copy records pertinent to this study. It is necessary for them to review study data, portions of study subject records and information so that they can follow the study progress, which may include without limitation:

- Monitor the accuracy and completeness of the study
- Perform scientific analysis and develop the medical product
- And/or obtain approval to market the medical products in the USA, Canada, EEA, and other countries.

Any information about subjects that leaves the institution conducting the study will be modified to remove certain information that could identify the subject (e.g., subject's name, age on the day of enrollment, address, and hospital number) and only be identifiable by a study ID code. Study data provided to SJM that is published in medical journals and/or presented at scientific conferences will not allow the identification of study subjects.

The results of the study will be made available to SJM and its affiliates (located in the U.S.A., EEA, Canada, and other countries) and other people who work for SJM to provide services related to the device and this study and study center.

A summary of the information on all subjects may be provided to governmental agencies (including regulatory agencies), regulatory authorities in the U.S.A., Canada, EEA and other countries who may also need to review study data and portions of medical records. Results from this study may also be published in scientific journals or presented at conferences as an oral or poster presentation; however, the identity of a study subject will not be disclosed.

9 Document Retention

The Principal Investigator (PI) shall maintain all essential clinical investigation documents from prior, during and (as specified) after the clinical investigation on file at the site for a minimum of 15 years after the termination of this investigation, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the sponsor prior to destroying or archiving off-site any records and reports pertaining to this investigation to ensure that they no longer need to be retained on-site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

All data and documents shall be made available on request of the relevant authorities in case of an audit.

The sponsor will archive and retain all essential clinical investigation documents from prior, during and (as specified) after the clinical investigation as per requirements.

10 Amendments to the Clinical Investigational Plan

The CIP, eCRFs, Patient Informed Consent form and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the CIP shall be agreed upon between the Sponsor and Principal Investigator, or the Coordinating Investigator.

The amendments to the CIP and the Patient Informed Consent shall be notified to, or approved by, the EC and regulatory authorities, if required. The version number and date of amendments shall be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be informed of the changes and a new Patient Informed Consent be signed and dated by the investigator and subject prior to the subject's next follow up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators by the Sponsor. This information will be incorporated by the Sponsor when an amendment occurs.

11 Publication Policy

The results of the clinical investigation will be submitted, whether positive or negative for publication.

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor (if applicable).

If such a Publication Agreement is not signed by both parties as a separate agreement but as part of an overall Clinical Trial Agreement, the publication policy should be part of the Clinical Trial Agreement.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

12 Investigation Organization

12.1 Investigation Management / Sponsor

The organization, which takes responsibility for the initiation and/or implementation and coordination for the investigation is St. Jude Medical Cardiology Division Inc. d/b/a St. Jude Medical, Cardiovascular Division, Inc. with a principal place of business at 177 East County Road B, St. Paul, MN 55117 and with offices associated with the operation of this investigation located at: 5050 Nathan Lane Plymouth, MN 55442.

SJM will delegate responsibilities to the local SJM clinical entities in each country, as defined by the Power of Attorney.

Sponsor Responsibilities

Sponsor's responsibilities are in accordance with applicable guidelines. This includes but is not limited to the following activities:

- the design, overall conduct, analysis, and reporting of the results from this study
- Performing those actions necessary to protect the rights of subjects and the scientific credibility of the manner in which this study is conducted
- Selecting qualified study Investigators, study monitors and research staff
- Sign off the clinical investigational plan before the start of the investigation or after modifications to the CIP;
- Development of database;
- Selection of clinical investigators;
- Training of the clinical investigational sites;
- Activate the sites after receipt of the required documentation;
- Monitor the participating centers by reviewing collected data and investigation documentation for completeness and accuracy;
- Perform data analysis;
- Ensure that all adverse events and adverse device effects are reported and reviewed with the clinical investigator(s) and where appropriate that all serious adverse events and serious adverse device effects are reported to the relevant authorities and Ethics Committee(s) and/or safety monitoring committee(s);
- Maintain an updated list of principal investigators, investigational sites and institutions. This list shall be available upon request.
- SJM reserves the right to obtain data clarification and/or additional medical documentation on subjects enrolled in this study at any time during the subject participation and until the study is terminated or closed by study final report. An interim analysis may be completed at the discretion of the Sponsor.
- Blank, revision controlled CRFs and patient information sheet/patient consent form template
- Signed Study Agreements and completed Investigator Financial Disclosure information
- EC approval letters, including a copy of the approved information sheet and consent forms
- All correspondences relating to the conduct of this study between SJM and the study site, ECs, and Study Monitors
- CVs and professional licenses for all study personnel, if applicable

- Protocol/device related training records for all applicable study personnel
- Site personnel signatures and documentation of the Investigator's delegation of study related responsibilities
- List of EC voting members
- Investigator's Brochure
- Insurance certificate

12.2 Clinical Investigators

All parties participating in the conduct of the clinical investigation shall be qualified by education, training or experience to perform their tasks and this shall be documented appropriately.

The role of the Principal Investigator is to implement, supervise, and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.

All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation.

The Principal Investigator shall;

1. Be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation.
2. Principal investigator and investigation team members shall provide signed and dated CVs and other relevant documentation,
3. Be experienced in the field of application and documented training of investigational device use under consideration,
4. Disclose potential conflicts of interest, including financial disclosure,
5. Be knowledgeable with the method of obtaining informed consent.

Investigator's responsibilities

By agreeing to this Clinical Investigation Plan, the investigators accept to allow monitoring, audits, Ethics Committee review, and regulatory inspections that are related to the investigation. They also agree to provide authorized individuals with direct access to source data and documentation as well as the right to copy records, provided such activities do not violate subject consent and subject data confidentiality.

A Principal Investigator should have experience in and/or will be responsible for:

- Providing signed Clinical Trial Agreement and appropriate appendices; as wll as other study specific agreements;
- Providing the Sponsor with copies of any clinical-investigation-related communications between the Principal Investigator and the EC;
- Screening and selecting appropriate subjects;
- Providing appropriate Ethics Committees Approved Patient Informed Consent;

- Conducting the clinical investigation in accordance with the signed agreement with St Jude Medical, the investigation plan, all applicable laws and regulations, and any conditions of approval imposed by the appropriate Ethics Committees or applicable regulatory authorities where the investigation is performed;
- Collecting and archiving of source data obtained prior to procedure, during procedure, at follow-up examinations and after the investigation has been completed;
- Strict adherence to the CIP testing requirements to provide for optimal safety and efficacious use of the device under clinical investigation;
- Adequate safety reporting;
- Supporting the monitor, and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the case report forms where inconsistencies or missing values are identified;
- Notifying the Sponsor of any deviations from the protocol
- Sign off the final version of the clinical investigation plan and amendments to the CIP

It is acceptable for the Principal Investigator to delegate one or more functions to an associate or co-investigator, however, the Principal Investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigational plan and collecting all required data. This delegation of specific functions shall be documented on the Signature and Delegation List (provided by Sponsor). The investigation is not transferable to other centers attended by the investigator unless prior approval is obtained from SJM.

Clinical Coordinating Investigator

In addition to the responsibilities of the investigators, the Clinical Coordinating Investigator will:

- Sign off the final version of the investigational plan and after modifications to the CIP;
- Act as main contact for all investigators in case of medical questions related to the conduct of the investigation.

The following investigators have been appointed by the Sponsor as the Clinical Coordinating Investigators:

Professor Stephen Worthley, M.B., B.S., Ph.D.,
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12.3 Committees

12.3.1 Steering Committee (SC)

The SC is championed by the Clinical Coordinating Investigator (CCI) Prof. Worthley. This committee will be actively involved in the investigation, and review its progress at regular intervals. The Steering Committee will serve as a decision making committee and assist with decisions along with the sponsor for the medical and scientific conduct of the study. The Steering Committee will operate in accordance with the steering committee charter. The Steering Committee will approve the CIP and any amendments (if applicable). At any time, this committee may recommend that the investigation be put on hold or even terminated for safety, ethical or other reasons. The Steering Committee will be composed of medical practitioners who are experts in the field of the proposed indication for the study.

12.3.2 Clinical Event Committee (CEC)

An independent Clinical Event Committee (CEC) will be utilized to regularly review study progress with regard to safety. Members of the CEC will include at a minimum, 3 physicians who are familiar with hypertension therapies including RF ablation of the renal artery. Physicians on the CEC will not participate in the investigation as investigators. The purpose of the CEC is to:

- Review and adjudicate all serious adverse events and adverse device effects as they occur over the course of the clinical investigation
- Determine severity classification and relationship to the device and procedure
- Provide oversight for issues affecting general subject welfare

The CEC will have a formalized charter that will detail a schedule for meeting times, explicit rules outlining the minimum amount of data required, process followed in order to assure appropriate and consistent classification of clinical events. CEC members will be provided clinical data and source documents to allow adjudication of events without subject, site or investigator identifying information. CEC decisions will be documented in meeting minutes, which will be maintained in the study master file

12.4 Outsourcing of duties and functions

The sponsor may transfer any or all of the duties and functions related to the clinical investigation, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation shall reside with the sponsor. All requirements applying to the sponsor shall also apply to the external organization inasmuch as this organization assumes the clinical-investigation-related duties and functions of the sponsor.

12.4.1 Power of Attorney (POA)

The POA delegates sponsor's responsibility for specified tasks to the country entities, divisions or designee, involved in the clinical project. The POA is signed and dated by appropriate parties. The POA can consist of, but is not limited to:

1. Ensure that the clinical agreements are prepared appropriately, comply with legal obligations and are signed/dated by all parties;
2. Ensure that essential documents to activate the center are collected and maintained in the ISB;
3. Activate the centers and manage the centers throughout the duration and close of the investigation;
4. Report Adverse Events to relevant authorities
5. Ensure that subject data relevant to the investigation is referenced in the hospital records, collected and provided to Sponsor

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Appendix A: Office Blood Pressure Measurement

Office Blood Pressure Visits: Baseline, Discharge, 1M, 6M, 12M, 24M, 36M, 48M, 60M

Office blood pressure corresponds to the blood pressure measured by the doctor or the nurse/staff in the office or in the clinic during the subject visit.

Operating Procedures

Subject Instruction:

- Avoid caffeine, exercise and smoking at least 30 minutes prior to the blood pressure measurements

Administrator Instructions:

- Allow the subject to sit quietly for at least 5 minutes in a chair, with feet on the floor before beginning the blood pressure measurements.
- The subject's arm should be supported.
- Have the cuff at the heart level of the subject
- Blood pressure measured with a validated device to identify systolic and diastolic BP. Take three blood pressure measurements (ESC/ESH minimum of two) spaced by 1 to 2 minutes and record the measured values into the worksheet.
- The average of these three measured values determine the office blood pressure of the subject at this visit

Appendix B: 24 Hour Ambulatory Blood Pressure

The standard 24-hour ambulatory blood pressure Visits: Baseline, 6M, 12M, 24M, 36M, 48M, 60M

In the 24-hour blood pressure monitoring, the blood pressure of patient will be measured every 30 minutes during the daytime and every 60 minutes during the night time.

Operating Procedures (ESC and ESH Guidelines)[55]

Patient Instructions:

- Engage in normal activities, but to refrain from strenuous exercise during the measurements
- Keep the arm extended and still during cuff inflations
- Record into the 24-Hour Ambulatory Blood Pressure Recording Log any unusual events that may occur during the 24-hour monitoring

Administrator Instructions:

- Set-up the time interval of automatic blood pressure measurement for patient during the visit
- Ensure that at least two measurements per hour are taken during the person's usual waking hours (for example, between 08:00 and 22:00).
- The average value of at least 14 measurements taken during the person's usual waking hours should be used for calculation of mean.
- Ensure that at least one measurement per hour is taken during the person's usual sleeping hours (for example, between 22:00 and 8:00).
- The average value of at least 8 measurements taken during the person's usual sleeping hours should be used for calculation of mean.

Appendix C: NYHA Assessment Classifications[57]

NYHA Assessment will be evaluated at baseline, 1M, 6M, 24M, and 60M follow-up visit and should be classified based on the following definitions:

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Appendix D: Patient Information Sheet and Consent Form Template

PATIENT INFORMATION SHEET AND CONSENT FORM

Full title: EnligHTN II - IntErnational non-randomized, single-arm, long-term follow-up study of patients with uncontrolled HyperTensioN
Study Location:
Principal Investigator:
Sponsor: St. Jude Medical Cardiology Division, Inc. d/b/a St Jude Medical Cardiovascular Division, Inc.

1. Introduction

You are invited to take part in a research study because you have high blood pressure that is difficult to treat with medication. The research project is testing a device and a treatment for high blood pressure. The treatment is called renal denervation.
This Patient Information Sheet and Consent Form tells you about the research study. It will explain the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully and ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this study is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to have the tests and treatments that are described;
- consent to the use of your personal and health information as described.

You will be given a copy of this Patient Information Sheet and Consent Form to keep.

2. Purpose and Description of the Research

The purpose of this study is to collect information regarding the effectiveness of a procedure used to treat high blood pressure. The procedure is called renal denervation. It involves placing a catheter (long thin round solid tube capable of conducting radiofrequency energy) in your renal (kidney) artery and heating the tip of the catheter to damage the tissue in particular areas of the artery. This tissue is known to contribute to high blood pressure. Previous studies have shown that this treatment was effective in lowering blood pressure. However, more clinical data is required to confirm these results.

The sponsor of the study is the maker of the device. The EnligHTN Renal Denervation System, has been approved for use, and is commercially available. None of the tests and procedures in this study are experimental.

Approximately 500 patients will take part in the project at up to 40 centers located in about 17 different countries. All patients who are eligible and have the appropriate artery anatomy will have the renal denervation procedure.

Your participation in this study will be approximately 5 years. This study will collect data from you medical history including past treatment for your high blood pressure, the renal denervation procedure, and follow-up study visits.

3. Study Tests and Procedures

If you agree to participate, the investigator will record your current medications and blood pressure measurements, demographics, and physical assessment for height and weight. The doctor will also complete a NYHA assessment, which is an evaluation to rank the limitations in your daily activities based on shortness of breath and chest pain.

Your doctor will need to confirm your blood pressure. You may be asked to wear a 24 hour blood pressure recording device. This test involves taking your blood pressure at 30 minute intervals throughout the day and at 60 minute intervals during the night using a portable monitor. The monitor itself is a small box approximately 3cm x 11cm x 9cm in dimension. The monitor is worn on a belt around your waist and there will be a tube connecting the box to a cuff which is worn on your arm. The monitor automatically inflates every 30 minutes during the day (or every 60 minutes during the night) over 24 hours. When the cuff begins to inflate you are required to keep your arm extended and still until the cuff deflates. You will also be asked to record unusual events during these 24 hours on a log. It is advisable that you arrange to wear the monitor on a day when you can go about your usual activities, including attending work but refrain from doing strenuous exercise. You will not be able to shower or bathe until the monitor is removed the following day. It is important to return the monitor at this time.

You will be asked to record your medication use for 2 weeks prior to the renal denervation procedure. This will require you to come back to see your doctor for a confirmatory visit to make sure you are eligible for the procedure.

During this visit, you will also be asked to complete a Quality of Life Questionnaire to assess your general wellbeing, and to provide a blood sample (about 10-15mL) and urine sample to

measure how well your kidneys are working. You will be asked not to eat or drink anything except water after 10 pm the night prior to the visit.

[Only applicable at 6 selected centers. Please remove section in italics if center won't perform TTE.]

You will have an echocardiogram (TTE) and may experience some discomfort from the echo transponder (wand) pushing on your chest during the echocardiogram test. You may be asked to hold very still, breathe in and out very slowly, hold your breath, or lie on your left side during an echocardiogram. You will not have pain during this procedure; however, you may feel uncomfortable from lying still or from the transducer (a small instrument that looks like a microphone) being pressed firmly against your chest to obtain pictures of your heart. Although most people do not experience any discomfort from ultrasound tests, if you have severe difficulty breathing or cannot lie flat for a long examination, please talk to your doctor or the technician performing your procedure about any concerns you have

You will have a test to assess the structure of your renal arteries. You may have a painless Abdominal Ultrasound, a Computed Axial Tomography (CT) scan, a Magnetic Resonance Angiogram (MRA) or an Angiogram to assess your renal arteries. The following helps explain each test:

- If you have an Abdominal Ultrasound you will be lying down for the procedure. A clear, water-based conducting gel is applied to the skin over the abdomen. This helps with the transmission of the sound waves. A handheld probe called a transducer is then moved over the abdomen. You may be asked to change position so that the health care provider can examine different areas. You may also be asked to hold your breath for short periods of time during the examination. The procedure usually takes less than 30 minutes
- A CT scan combines special x-ray equipment to produce multiple images or pictures of the inside of the body. These images of the area being studied can then be examined on a computer monitor. During the test, you will lie on a table that is attached to the CT scanner, which is a large doughnut-shaped machine. The CT scanner sends X-rays through the body area being studied. Each rotation of the scanner provides a picture of the area being studied. In some cases, a dye called contrast material may be used. It may be put in a vein in your arm to see the area better. For some types of CT scans you drink the dye. The dye makes structures and organs easier to see on the CT pictures. This procedure can take 15 to 30 minutes.
- Most Magnetic Resonance Angiograms (MRA) exams are typically painless. You will be positioned on the moveable examination table. Straps may be used to help you stay still and maintain the correct position during imaging. It is normal for the area of your body being imaged to feel slightly warm, but if it bothers you, notify the radiologist or technologist. It is important that you remain perfectly still while the images are being recorded. MRA exams generally include multiple runs (sequences), each typically a few seconds to a few minutes at a time. The entire examination is usually completed within one hour. If a contrast material will be used in the MRA exam, a nurse or technologist will insert an intravenous (IV) line into a vein in your hand or arm. It is normal to feel coolness and a flushing for a minute or two when the contrast material is injected.

- An Angiogram is a special kind of x-ray. You will receive a local anaesthetic and then a small puncture will be made through the skin into the femoral artery on your upper thigh (groin).With the aid of fluoroscopy (x-ray that uses a fluorescent screen) a thin, flexible tube called a catheter will be threaded to the renal artery. A special dye will be injected through the catheter so the renal artery will show up clearer on the x-ray. You may be presented with a separate consent form that describes the renal artery angiogram procedure in greater detail.

If the structure of your renal arteries is appropriate for the study, you will continue to have the renal denervation procedure. If the structure of your renal arteries is not appropriate, you will not have the renal denervation procedure. However, you will still need to attend a 1 month follow-up visit. At this visit a physical assessment and office blood pressure will be performed.

The renal denervation procedure will create a small opening (puncture) in an artery in your leg near the groin so that tubes, called catheters, can be introduced into your renal arteries. The catheter will deliver heat (using radiofrequency energy) and ablate (damage) the nerves from inside the artery. The investigator will repeat the ablation until he/she feels appropriate. After ablation, the catheter will be placed in the second renal artery to ablate the nerves there.

Once the renal angiogram and renal denervation procedure are complete, the catheter will be slowly and carefully removed and pressure will be applied or a device used in order to help the arterial puncture to reseal itself.

After the procedure you will be transferred for observation and you may stay in the hospital overnight. While you are in hospital your vital signs will be recorded continuously and your blood pressure will be recorded every 4 hours after the procedure until discharge or for a maximum of 24 hours. Also, any unfavorable or unintended symptoms or findings you may have (adverse events) will be recorded and treated as appropriate.

Prior to discharge from hospital your blood pressure and the medications you are taking will be recorded.

After the renal denervation procedure, you will return for a follow-up visit at 1 month, 6 months, 12 months (1 year), 24 months (2 year), 36 months (3 year), 48 months (4 year) and at 60 months (5 year).

During your follow up visits the following tests/assessments will be performed:

- Physical Assessment and medication review at every visit
- Office blood pressure measurements at every visit
- 24 hour Ambulatory Blood Pressure at 6, 12, 24, 36, 48 and 60 month visits
- Blood and urine samples will be collected at 6, 12, 24 and 60 month visits. You will be asked to not to eat or drink anything except water after 10pm the night prior to the 6 month visit.
- [Only applicable at 6 selected centers. Please remove this point if center won't perform TTE.] Echocardiogram (TTE) at the 1, 6, 24 and 60 month visits
- NYHA Assessment at the 1, 6, 24 and 60 month visits
- Quality of Life Questionnaire at 1, 6, 24 and 60 month visits

- Renal artery evaluation at 6, 24 and 60 month visits

4. Study Related Risks

There are risks, discomforts, and inconveniences associated with any research study that you should consider before deciding to participate in this study. You should talk with the investigator if you have any questions.

Precautions will be taken to ensure that side effects, should they occur, will be acted upon immediately.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. Tell your doctor if you have any problems. Your doctor will discuss the best way of managing any side effects with you.

Having blood taken may cause some discomfort or bruising. Sometimes, the blood vessel may swell, or blood may clot in the blood vessel, or the spot from which blood is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated.

The renal denervation is an interventional approach, and as such carries some potential risks, which may include but are not limited to the following:

- Acute renal injury (renal infarction, renal hematoma)
- Renal vascular injury (renal artery dissection, renal artery thrombosis, renal artery stenosis)
- Collateral tissue injury
- Malignant or accelerated hypertension
- Symptomatic hypotension
- Access site complications (arteriovenous fistula, access site thrombosis, embolisation, pseudo-aneurysm, hematoma, limb ischemia, femoral nerve injury, or seroma)
- Disseminated intravascular coagulation
- Infection (access site infection or systemic infection)
- Renal failure
- Decompensated heart failure
- Myocardial infarction
- Neurologic event (acute ischemic or hemorrhagic brain injury)
- Respiratory compromise
- Pain, including Back Pain
- Death
- Drug reactions
- Contrast allergies etc
- Bradycardia
- Vasospasms
- Vasovagal episodes

When you have CT scan or renal artery angiogram, you will be exposed to radiation. This research study involves exposure to a small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 25 mSv. The dose from

this study is comparable to that received from several computed tomography x-ray (CT) and nuclear medicine procedures. The benefits from the study should be weighed against the possible detrimental effects of radiation, including an increased risk of fatal cancer. In this particular study, the risk is moderate and the estimated risk of such harm is about 1 in 800. For comparison, this risk is about 200 times lower than the cancer mortality rate in the general population of about one case in every four people.

The effects of renal denervation procedure on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you may be required to undergo a pregnancy test prior to commencing the research project.

If you do become pregnant whilst participating in the study, you should advise your treating doctor immediately.

There may be other risks that are not known at this time. Tell your doctor immediately about any new or unusual symptoms that you get.

5. Potential Benefits

We cannot guarantee or promise that you will receive any benefits from this research. However, possible benefits may include a decrease in your blood pressure, which may also have beneficial effects on your heart. It should be noted that less than 20% of patients in previous studies had no significant reduction in blood pressure. The information gathered from the study will add to the understanding of the treatment options for patients with high blood pressure. This knowledge may advance medical science and may, in turn, benefit other patients with high blood pressure.

6. Alternative Therapy

Participation in this study is not your only option. Your other options may include changing your blood pressure medications. Discuss these options with your doctor before deciding whether or not to take part in this study. This treatment differs from standard treatment as it involves a procedure rather than the use of medications.

While you are participating in this research project, you may not be able to take some or all of the medications or treatments that you have been taking for your condition or for other reasons. It is important to tell your doctor and the research staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your doctor about any changes to these during your participation in the research. Also ask your doctor to explain to you which treatments or medications may be taken while you are participating in this research project.

7. Study Related Injuries

Your study doctor and St. Jude Medical will take all reasonable measures to prevent any injury or illness that might result from your participation in this research. In the event you are injured or

become ill as a direct result of your participation, medical care and treatment will be available at this hospital.

Should physical injury with a link to the study occur, medical care, including first aid, emergency treatment, and follow-up care will be available as needed. You may be expected to pay for such treatment or seek reimbursement from your health care coverage.

If you followed all the instructions of the study and are injured during the study as a direct result of your participation in the study, SJM agrees to pay for reasonable and necessary, and otherwise non-covered treatment of injuries or adverse reactions which are a direct result of protocol-related procedures, which you would not have received as part of routine medical care, or that are caused by a defect or malfunction of the device during the study. SJM is not responsible for medical risks or conditions (including the natural progression or manifestation of your coronary disease or any underlying illness, whether previously diagnosed or not) that you would face if you were not participating in the study. SJM is not responsible for the wrongdoing or action of any other party other than including any illness or injuries resulting from your failure to follow the study's instructions, including participation in all follow-up visits. The sponsor will maintain insurance in accordance with the applicable local laws.

8. Confidentiality

To help keep your medical records and personal information confidential only certain authorized people will have access to your records. These include without limitation researchers in your hospital who are part of this study, Sponsor and its affiliates and representatives of SJM that perform study-related services located in the U.S., European Economic Area and other countries. It is necessary for them to review your records so that they can follow the study progress. A summary of the information on all patients may be provided to governmental agencies (including regulatory agencies); regulatory authorities in the U.S., European Economic Area and other countries who may also need to review your medical records. Information from this study may also be published in medical journals. However, your name and any other information that could identify you will never be used.

Your personal data, including medical and health information, will be processed both by computer and manually, during and after the study by SJM, and its affiliates, its designated third party data processors, the Ethics Committee, the institution, the Investigators and other health personnel involved in the study for the purposes of this Trial. Personal data about you will be key-coded so as not to permit your identification, except if necessary for the purpose of the trial, for regulatory inspections, and to comply with reporting obligations.

The data may be used for additional medical or scientific research projects in the future, publication in scientific journals, and obtaining regulatory approvals for the studied device. Data may, if necessary for the above purposes, be communicated to the processors, regulatory authorities and Ethics Committees located countries of the European Economic Area ("EEA"), in the United States of America ("US") and governmental agencies (including regulatory agencies) in other countries. Some of the non-EEA countries to which your data may be transferred may not offer an adequate level of protection of privacy of personal data. SJM has taken security measures to ensure your personal data will be processed and used in a confidential way.

You understand that your personal data, including but not limited to medical findings, is to be collected, stored and analyzed in the scope of this clinical trial. The information on your state of health will be used in accordance with the applicable statutory provisions and the use requires the following freely given declaration of consent prior to the participation in the clinical trial, i.e. without your below consent, you cannot participate in the clinical trial.

• You agree that, in the scope of this clinical trial, your personal data, including but not limited to information on your state of health, is collected and stored both in paper form and on electronic data carriers at the clinic in charge. If necessary, the collected data may be transmitted in anonymous form:

a) to the clinic, the sponsor or its designee for scientific evaluation purposes,
b) in case of adverse events: to the clinic, the sponsor and the competent regional authority.

• You understand and agree that your personal data may be transferred outside of the European Economic Area, including the United States for purposes that include, without limitation, processing monitoring, auditing and control of the study or the conduct of inspections by the relevant authorities, medical product development, additional scientific analysis of the study data, obtaining approval to use and market medical products resulting from, or related to the study. You understand that the data protection laws outside the European Economic Area may not be as strict as in your own country.

• You further agree that authorized representatives of the sponsor bound to secrecy as well as the competent supervisory authorities may access your personal data, including but not limited to your health data, kept by the investigator to the extent that this is required for the verification of the proper performance of the study. For this purpose, you hereby release the investigator from your medical confidentiality obligation.

• You have been advised of your right to terminate your participation in the clinical trial at any time. In the event that you revoke your consent to participate in the study, you are entitled to request the deletion of all your personal data stored until such point in time.

• You agree that your data will be retained for a period of at least fifteen years (or longer if required by local country laws) following the termination or discontinuation of the trial. After that, your personal data will be deleted unless required otherwise by statutory, by-law or contractual provisions.

You have a right to gain access and to correct inaccuracies in information about you held by SJM.

By signing the Patient Consent Form, you expressly consent to the collection, use, review and disclosure of such information.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

9. Compensation (medical/financial)

You will not be paid for taking part in the study. However, you will not be charged the costs specifically related to the study. The costs not specifically related to the study will be charged and reimbursed as usually by your health care coverage. .

10. Study Questions

We hope this answers your questions concerning the proposed evaluation, but if you have any questions about this research you should contact your doctor ("the Investigator") (tel:_____) or the Hospital department. If you have questions about your rights as a research subject you should contact the Ethics Committee at [*telephone #*]. You can also write to the Ethics Committee at [*address*].

11. Study Withdrawal

Your participation in the study is entirely voluntary. If you decide to participate, you may quit the study at any time without a reason. Just tell your doctor you do not wish to continue your participation. If you leave the study before the final regularly scheduled visit, you may be asked by the study doctor to make a final visit. It is recommended you continue to see your regular doctor. There will be no penalty or loss of any benefits to which you are otherwise entitled if you decide not to continue with the study. When you withdraw from the study, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others as described in this form Your doctor or SJM may also stop your participation at any time, without your consent, due to medical conditions or other factors that affect your study eligibility.

12. New Findings

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and your doctor will discuss whether this new information affects you.

Patient Informed Consent (PIC) Template

Full title: EnligHTN II - IntErnational non-randomized, single-arm, long-term follow-up study of patients with uncontrolled HyperTensioN
Study Location:
Principal Investigator:
Sponsor: St. Jude Medical Medical Cardiology Division, Inc. d/b/a St Jude Medical Cardiovascular Division, Inc.

Are you currently participating in other research studies? ___Yes ___No

Statement of Informed Consent:

- I understand that my participation in this study is voluntary
- I understand that I am free to refuse to participate in this study without giving reason and without my medical or legal rights being affected
- I understand that I am free to withdraw from this study at any time without giving reason and without my medical care or legal rights being affected.
- I understand that data collected during this study prior to the withdrawal will be used in the analysis and communicated in publication.
- I understand that information gained during the study maybe published, and I will not be identified and personal data will remain confidential.
- I understand that my health information may be stored in a database and study results may be looked at, used, and disclosed by the investigators, St. Jude Medical, Cardiology Division, Inc. d/b/a (doing business as) St. Jude Medical, Cardiovascular Division, Inc., a U.S. company, and its affiliates (located in the USA and EEA and other countries, and other people who work for St. Jude Medical to provide services related to the device and this study (SJM) regulatory authorities, and the Ethics Committee, when it is relevant to my taking part in this research. I give permission for these individuals to have access and use to my medical information for this study.
- I understand that photograph and video recordings (after being anoymised) may be taken during the operation of the device during the study and used for this study and future research.
- I understand that my information will not be used for any mailing lists or sold to anyone for marketing purposes.
- I understand I have a right of access and a right to correct any inaccuracies in information about me .
- I understand the risks associated with this study.
- I understand that I may not benefit from taking part in the study.
- I understand that this study was reviewed by the Ethics Committee.
- I understand how to contact the research team if I have concerns about the study

Acknowledgement of the information provided:

- I confirm that I have read and understand the information presented for this study.
- I have had the opportunity to discuss participation in the study and have had the opportunity to ask questions and have them answered.

Informed Consent Agreement:

- I agree to participate in this study and to comply with the procedures related to it.
- I give my permission to have my general practitioner informed of my participation in this study.
- I give my permission to access my records by the investigator, sponsor(and its designees), ethics committee, and regulatory authorities for data for the purpose of this study.

Subject Signature

Subject Signature _____ Date_____

Printed Name of Subject _____

Subject's Legal Representative (if necessary) Signature

Signature _____ Date_____

Printed Name of Legal Representative_____

Person Conducting Informed Consent Discussion

Signature _____ Date _____

Printed Name _____

Appendix E: Abbreviations

Abbreviation	Term
ABP	Ambulatory Blood Pressure
ADE	Adverse Device Effect
AE	Adverse Event
ANZ	Australia – New Zealand
ASADE	Anticipated Serious Adverse Device Effect
BP	Blood Pressure
CA	Competent Authority
CCI	Clinical Coordination Investigator
CIP	Clinical Investigational Plan
CRF	Case Report Form
CPRB	Clinical Project Review Board
CT	Computed Axial Tomography
DCC	Data Cleaning Convention
DD	Device Deficiency
DMP	Data Management Plan
DVP	Data Validation Procedure
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMEAC	Europe, Middle East, Africa, Canada
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GP	General Practitioner
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
ISB	Investigator Site Binder
ISO	International Organization for Standardization
MDRD	Modification of Diet in Renal Disease
MP	Monitoring Plan
MR	Magnetic Resonance
NAP	Not Applicable
PI	Principal Investigator
POA	Power of Attorney
RDC	Remote Data Capture
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

Appendix F: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

- The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
- The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
- Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

- It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

- The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

- Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

- In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

- The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

- In medical practice and in medical research, most interventions involve risks and burdens.

- Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

- It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

- Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

- The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding,

sponsors, institutional affiliations, and other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

- The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

- Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

- Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

- Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

- Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

- Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

- Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

- Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

- In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

- For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

- When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the

physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

- For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

- When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

- Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

- The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

- At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

- The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

- In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix G: Data Collection Method (EDC)

Sponsor/Investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each subject. Source documents include all original records from which eCRFs derive their data.

Access to eCRF application

The eCRF application is accessed through the internet and requires the use of a personal user account and password.

The following documents and information are required prior to receipt of personnel user account and password:

- Current signed and dated CV
- Completed Signature and Delegation List
- Documented training
- Email address and telephone

Personal user account and password are provided via email. User account and password are confidential and personal. They are not to be shared with other people.

The first time the application is accessed, the password will need to be changed.
If the password is forgotten and/or lost, a new password can be provided via email by following the instructions on the webpage.

Each center must be authorized to start enrolling patients in the investigation before access privileges to the application is made available.

Access privileges are based on the tasks assigned on the Signature and Delegation List and will be either:

- Data entry and review
- Data entry, review and sign off

All eCRFs are completed, saved (‘save complete’) and approved by an investigator in a timely manner.

Appendix H: List of Case Report Forms

Data Points Provided Under Separate Cover

- Screening: Inclusion/Exclusion Criteria
- Baseline/Medical History Form
- Confirmatory Visit Form
- Physical Assessment/Office Blood Pressure Form
- 24 Hour Ambulatory Blood Pressure Form
- Echocardiography Form
- Blood/Urine Lab Form: Serum Creatinine, eGFR, Hemoglobin A1c, Fasting Glucose, Fasting Insulin and Albumin-Creatinine Ratio
- Medications Log
- Renal Artery Evaluation Form
- Renal Denervation Procedure Form
- Additional Arteries From
- Post Procedure and Discharge Form
- Adverse Event Form
- Death Form
- Deviation Form
- Termination Form