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EnligHTN European Observational Study

Clinical Investigation Plan (CIP)

Amendment 1

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Revision History				
Amendment N°	Project Version	Date	Rationale	Details
NAP	V1.0	03May2013	First release of CIP	NAP
1	V2.0	25Mar2014	Main Changes to the CIP: • To adapt the indication according to the updated Instructions for EnligHTN ablation catheter • To remove the need for a Clinical Event Committee (CEC)	See Summary of Changes

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1 Summary of Changes

Change 1:
Modification of the Inclusion and Exclusion Criteria following the change of indication from 'hypertension' to 'resistant hypertension' in the Instructions for Use. Patients unable to take 3 anti-hypertensive medications because of intolerance cannot be enrolled following implementation of this amendment.

Change 2:
Update of the intended use of the ablation catheter from 'hypertension' to 'resistant hypertension'

Change 3:
Clarification of tests and assessments performed per standard of care before the baseline visit, which can be used for the study.

Change 4:
Modification of need to collect the Urine albumin-creatinine ratio. Will only be collected if lab test was performed per standard of care.

Change 5:
Removal of reference of an Investigator Brochure, as the device has been marketed and the Instructions for Use should do.

Change 6:
Removal of the Clinical Event Committee (CEC) as usually not required for an Observational Study. The safety oversight including classification of events and determination of relationship of events to device and procedure will be done by SJM.

Change 7:
Replacement of Appendix B: Declaration of Helsinki with the version of the 64th WMA General Assembly, Oct 2013.

Other changes:
Corrections of typos and grammatical errors having no impact on the content of the protocol; Updates to section numbers.

Change number, Paragraph(s) & Page(s) (referring to CIP v2.0)	**CIP V1.0**	**CIP V2.0 Amendment 1**
Change 1: Synopsis (p.11) and Inclusion and Exclusion criteria (p.18)	Subject has established hypertension (diagnosed ≥12 months prior to baseline) and is on a guideline based drug regimen at a stable (≥ 14 days) 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-I/ARB, Calcium Channel Blockers, Beta Blockers, or diuretic) and is unable to take 3 anti-hypertensive drugs	Subject has established hypertension (diagnosed ≥12 months prior to baseline) and is on a guideline based drug regimen at a stable (≥ 14 days) and a fully tolerated dose consisting of ≥3 anti-hypertensive medications (including 1 diuretic)
Change 2: Intended Use (p.19)	The ablation catheter is indicated for use in renal denervation procedures for the treatment of hypertension.	The ablation catheter is indicated for use in renal denervation procedures for the treatment of resistant hypertension.
Change 3: Enrollment/ Baseline Visit (p.21)	All baseline activities are performed after the patient is enrolled in the investigation. Tests and other required assessments performed as standard of care before the baseline visit can be used if done within 90 days prior to procedure.	All baseline activities are performed after the patient is enrolled in the investigation. Ambulatory Blood Pressure Recordings performed as standard of care within 2 weeks before the baseline visit can be used. Other tests and required assessments performed as standard of care before the baseline visit can be used if done within 90 days prior to procedure.

Change 4: Procedures (p.22) and Blood/Urine Analysis (p.24)	Urine albumin-creatinine ratios are required per Table 1 Data/CRF collection. Blood and urine samples will be drawn and analyzed. The following results will be collected: • Serum Creatinine • eGFR • Urine albumin-creatinine ratio • Pregnancy test (if applicable)	Updated Table 1 Data/CRF collection to clarify that Urine albumin-creatinine ratios will only be collected if done per clinical routine. Blood and urine samples will be drawn and analyzed. The following results will be collected: • Serum Creatinine • eGFR • Urine albumin-creatinine ratio (if available per standard of care) • Pregnancy test (if applicable)
Change 5: Anticipated Adverse Events and Adverse Device Effects (p.34)	Adverse events potentially associated with the use of the EnligHTN Renal Denervation System and their potential complications are documented in the Instructions for Use (IFU) and the Investigator Brochure (IB). Both documents are available upon request.	Adverse events potentially associated with the use of the EnligHTN Renal Denervation System and their potential complications are documented in the Instructions for Use (IFU) which is available upon request.

Change 6: Clinical Event Committee	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 serious adverse events and adverse device effects as specified in the CEC charter • 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 and processes 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.	Section has been removed.

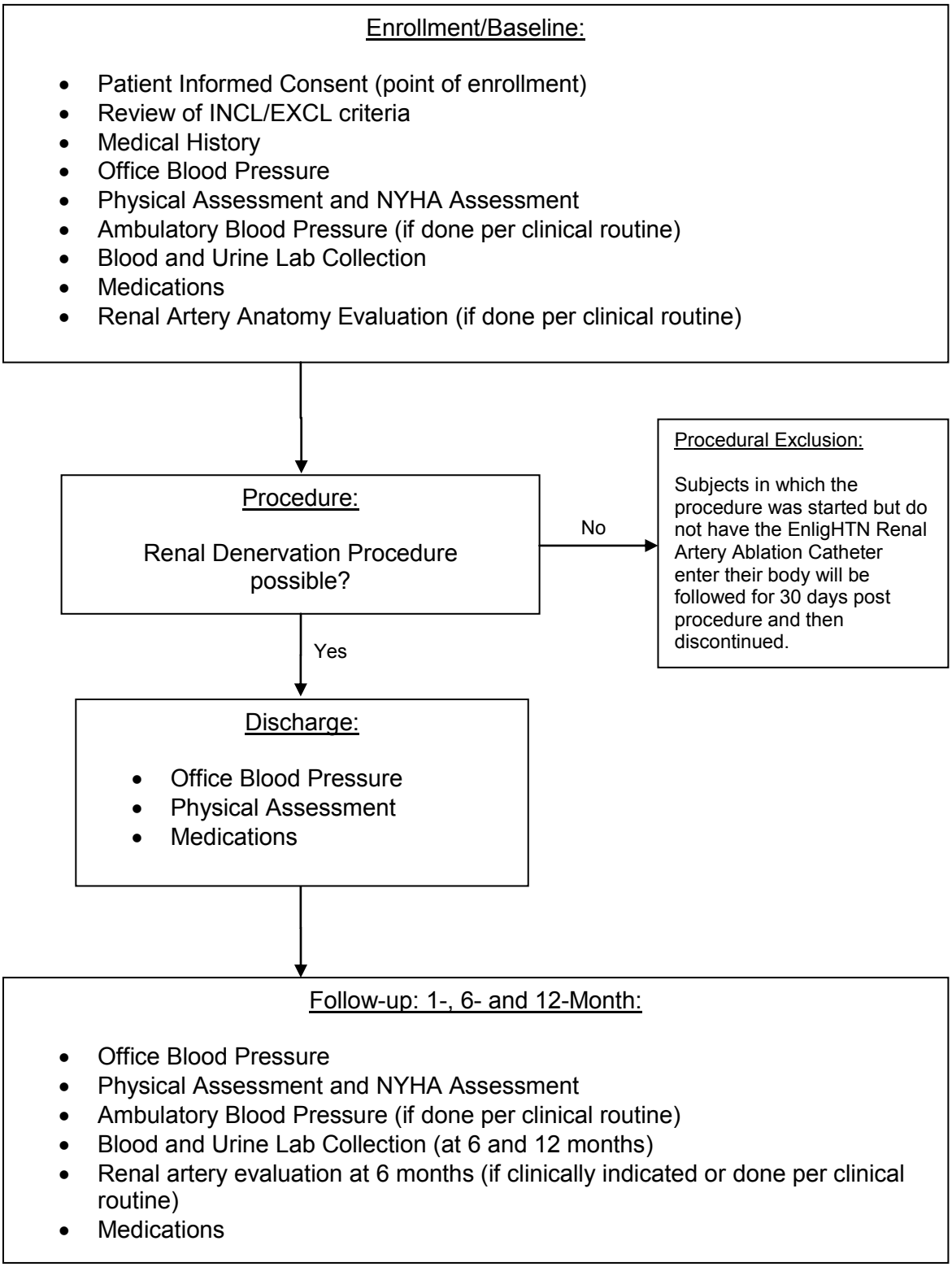
2 Synopsis

Title:	EnligHTN European Observational Study
Acronym:	EnligHTN European Obs Study
Purpose:	The purpose of this observational study is to further evaluate the safety and performance of the EnligHTN™ Renal Denervation System in the treatment of patients with uncontrolled hypertension in clinical routine practice.
Objectives:	Primary: Mean reduction in office Systolic Blood Pressure at 6 months Secondary: ○ Acute (30 days) ○ Safety: ▪ Assessment of peri-procedural adverse events up until 30 days post procedure ○ Performance: ▪ Mean reduction in office Systolic and Diastolic Blood Pressure at 1 month ▪ Mean reduction in ambulatory Systolic and Diastolic Blood Pressure at 1 month ▪ Percentage of subjects achieving office Systolic Blood Pressure < 140 mmHg at 1 month ○ Mid to long term (6 and 12 months) ○ Safety: ▪ Renal function change based on eGFR at 6 and 12 months ▪ Assessment of renovascular safety as measured by new renal artery stenosis and aneurysm at the site of ablation at 6 months ○ Performance: ▪ Mean reduction in office Systolic Blood Pressure at 12 months ▪ Mean reduction in office Diastolic Blood Pressure at 6 and 12 months ▪ Mean reduction in ambulatory Systolic and Diastolic Blood Pressure at 6 and 12 months ▪ Percentage of subjects achieving office Systolic Blood Pressure < 140 mmHg at 6 and at 12 months
Design:	This is a post market, multi-center, open label, observational study. Approximately 500 subjects with uncontrolled hypertension will undergo renal artery ablation at approximately 50 investigational sites located in Europe and the Middle-East, and will be followed for 1 year post procedure.
	The expected duration of the investigation will be approximately 4 years.

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 participating countries. Further CE marked released devices for renal denervation will be used in this investigation as they become available on the market.
Patient Population:	The patient population enrolled in this investigation will consist of males and females with uncontrolled hypertension who meet all inclusion criteria, and none of the exclusion criteria.
Patient Screening:	<u>Patient Screening:</u> Patients who do meet all inclusion criteria and don't meet any of the exclusion criteria are eligible to participate. Eligible patients 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 of the investigation once he/she has been fully informed about the investigation, has agreed to participate, and signed & dated the Patient Informed Consent (PIC) form. <u>Inclusion Criteria</u> ○ Subject is planned to undergo a renal denervation procedure for the treatment of hypertension ○ 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 SBP ≥ 140 mmHg ○ Subject has established hypertension (diagnosed ≥12 months prior to baseline) and is on a guideline based drug regimen at a stable (≥ 14 days) and a fully tolerated dose consisting of ≥3 anti-hypertensive medications (including 1 diuretic) <u>Exclusion Criteria</u> ○ Subject has known 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 a history of hemodynamically significant valvular heart disease ○ Subject has blood clotting abnormalities ○ Subject life expectancy is < 12 months, as determined by the Study Investigator ○ Subject is participating in another clinical study which has the potential to impact his/her 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 known renal arteries with diameter(s) < 4 mm ○ Subject has an estimated GFR <45 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

Figure 1: Flow Chart



3 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, the blood pressure in these patients remained 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 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 resistant 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).[45-47,51]

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) is 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 1 March 2012 with a total of 46 patients having undergone the renal denervation procedure. Subjects will be followed for 24 months post procedure.

The 1 month clinical results from EnligHTN I were presented at the European Association of Percutaneous Cardiovascular Interventions, EuroPCR 2012 Congress 15-18 May 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 min. 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 ≥ 10 mmHg reduction in systolic Blood Pressure.

The 3 months 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 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 between baseline and 3 months was -9.9/-5.4 mmHg[52].

The 6 months primary endpoint results from EnligHTN I were presented at the American Heart Association meeting on 5 November 2012. Compared to baseline, Office and 24-hour

Ambulatory Systolic BP of the 45 subjects with available data (one subject had a missed visit) significantly decreased at all-time points (p value <0.0001). The average Office BP (mmHg) at baseline, 1 month, 3 months and 6 months post denervation procedure were 176/96, 148/87, 149/87, and 150/86 respectively. The resulting average Office BP (mmHg) reductions from baseline at 1 month, 3 months, and 6 months were -28/-10, -27/-10, and -26/-10. Over the follow-up period, as many as 80% of subjects had a reduction in office systolic BP of at least 10 mmHg or greater and up to 41% had an office BP of less than 140 mmHg. The average 24-hour Ambulatory BP (mmHg) reduction from baseline to 1 month, 3 months, and 6 months was -10/-5, -10/-5, and -10/-6 respectively. No serious vascular adverse events occurred during the procedure, including no renal artery damage (i.e. no renal artery dissections, aneurysms, new stenoses, or flow limiting renal artery vasospasms) or other vascular access complications. Minor peri-procedural events which were attributed to either the device or procedure were reported, including: non-flow limiting vasospasms, site hematomas, and vasovagal episodes. All minor events attributed to the device and/or procedure have resolved without further clinical sequelae.

Due to promising clinical evidence, this new therapeutic approach is likely to find a quick adoption. This EnligHTN observational study is designed to collect more data, critical to the benefit of the therapy, within a routine clinical setting.

4 Investigational Design

4.1 Purpose

The purpose of this observational study is to further evaluate the performance and safety of the EnligHTN™ Renal Denervation System in the treatment of patients with uncontrolled hypertension in clinical routine practice.

4.2 Objectives

Primary Objective

The primary objective will be to describe the mean reduction in office Systolic Blood Pressure at 6 months.

Secondary Objectives

The secondary objectives are:

- Acute (30 days)
  - Safety:
    - Assessment of peri-procedural adverse events up until 30 days post procedure
  - Performance:
    - Mean reduction in office Systolic and Diastolic Blood Pressure at 1 month
    - Mean reduction in ambulatory Systolic and Diastolic Blood Pressure at 1 month
    - Percentage of subjects achieving office Systolic Blood Pressure < 140 mmHg at 1 month
- Mid to long term (6 and 12 months)
  - Safety:
    - Renal function change based on eGFR at 6 and 12 months
    - Assessment of renovascular safety as measured by new renal artery stenosis or aneurysm at the site of ablation at 6 months

- Performance:
  - Mean reduction in office Systolic Blood Pressure at 12 months
  - Mean reduction in office Diastolic Blood Pressure at 6 and 12 months
  - Mean reduction in Ambulatory Systolic and Diastolic Blood Pressure at 6 and 12 months
  - Percentage of subjects achieving office Systolic Blood Pressure < 140 mmHg at 6 and at 12 months

4.3 Investigational Type

This is a prospective, multicenter, observational study of the EnligHTN™ Renal Denervation System. Approximately 500 subjects with uncontrolled hypertension will undergo renal artery ablation at approximately 50 investigational sites located in Europe and the Middle-East, and will be followed for 1 year post procedure.

4.4 Patient Population

The patient population enrolled in this investigation will consist of male and female patients, 18 years of age or older, who meet all specified inclusion criteria and none of the exclusion criteria (Section 4.5).

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

4.5 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 and signed & dated the PIC form (Refer to section 6.6 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 enrollment.
All subjects enrolled in the study (including those withdrawn from the study 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.

Inclusion Criteria

- Subject is planned to undergo a renal denervation procedure for the treatment of hypertension
- 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 SBP ≥ 140 mmHg

- Subject has established hypertension (diagnosed ≥12 months prior to baseline) and is on a guideline based drug regimen at a stable (≥ 14 days) and a fully tolerated dose consisting of ≥3 anti-hypertensive medications (including 1 diuretic)

Exclusion Criteria

- Subject has known 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 a history of hemodynamically significant valvular heart disease
- Subject has blood clotting abnormalities
- 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 his/her 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 known renal arteries with diameter(s) < 4 mm
- Subject has an estimated GFR <45 mL/min per 1.73 m^2 using the MDRD formula
- Subject had a renal transplant or is awaiting a renal transplant

Procedural Exclusions:
Subjects who have been enrolled in the study, and in whom 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. These subjects will be followed for 30 days post procedure. The reason for the procedural exclusion will be documented on the Procedural CRF.

4.6 Expected duration of the Investigation

The expected duration of the investigation will be approximately 4 years.

4.7 Expected duration of each subject's participation

The expected duration of each subject's participation will be approximately 1 year.

4.8 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.

4.9 Estimated time needed to select this subject population

The estimated time needed to enroll the number of subjects will be approximately 24-36 months.

4.10 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 manufacturer of the EnligHTN™ Renal Denervation System is St. Jude Medical, Cardiovascular Division, 14901 DeVeau Place, Minnetonka, MN 55345-2126, USA

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

4.10.1 **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.

4.10.2 **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.

4.10.3 **EnligHTN™ Guiding Catheter (optional)**

The EnligHTN™ Guiding Catheter system is comprised of two components: a guiding catheter and a dilator. The guiding catheter is constructed of three 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.

Upon receiving CE mark, new generations of SJM devices for renal denervation may be used in this clinical investigation as they become available on the market.

4.11 Intended Use

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

5 Procedures

Table 1: Data/CRF Collection

Activity \ Visit	Enrollment / Baseline	Procedure	Discharge <72 hrs	1M ±14d	6M ±30d	12M ±60d
PIS & PIC	X					
Inclusion/Exclusion	X					
Medical History	X					
Office Blood Pressure	X		X	X	X	X
Physical Assessment	X		X	X	X	X
Ambulatory Blood Pressure	X[1,2]			X[1]	X[1]	X[1]
NYHA Assessment	X			X	X	X
Serum creatinine	X				X	X
Estimated GFR	X				X	X
Urine albumin-to-creatinine ratio	X[1]				X[1]	X[1]
Medications	X		X	X	X	X
Renal Artery Anatomy Evaluation	X[1]	X			X[1]	
Pregnancy Test (urine / blood)	X**					
Renal Denervation Procedure		X				
Adverse Event Assessment	**	**	**	**	**	**
CIP Deviation	**	**	**	**	**	**
Withdrawal/ Termination		**	**	**	**	**

(**) As applicable
(1) If done per clinical routine
(2) Ambulatory Blood Pressure Recordings of the last 2 weeks can be used

5.1 Enrollment/Baseline Visit

Prior to enrollment in the study, 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 6.6 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) form, 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 form and therefore has been enrolled in the investigation.

NOTE: As soon as the subject signs the Patient Informed Consent form, adverse events need to be reported according to the guidelines mentioned in Section 6.7.8.

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. Ambulatory Blood Pressure (ABP) recordings performed as standard of care within 2 weeks before the baseline visit can be used. Other tests and required assessments performed as standard of care before the baseline visit can be used if done within 90 days prior to procedure.

5.1.1 **Medical History**
A complete medical history of the subject will be reviewed and recorded including:

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

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

- Age
- Gender
- Height
- Weight

5.1.3 **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[49, 50].

5.1.4 **Ambulatory Blood Pressure**

When performed per standard of care, daytime mean ABP, night time mean ABP and 24 hour average ABP values will be collected. Recordings of the last two weeks can be used.

5.1.5 **Medication**

The subject's baseline medication regimen, including medication name, dose, and frequency will be reviewed and recorded, making note of those medications taken specific to the subject's hypertension therapy.

The investigator will assess that the subject was on a stable anti-hypertensive medication regimen for a period of at least 14 days prior to enrollment. This assessment will be left at 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 deemed clinically necessary.

Investigators will urge subject compliance to prescribed medical regimen throughout the trial. If the subject is non-compliant without medical rationale, the subject may be excluded.

5.1.6 **Blood/Urine Analysis**

Blood and urine samples will be drawn and analyzed. The following results will be collected:

- Serum Creatinine
- eGFR
- Urine albumin-creatinine ratio (if available per standard of care)
- Pregnancy test (if applicable)

5.1.7 **NYHA Assessment**

NYHA Assessment[53] will be evaluated at baseline and will be classified as the following:

- Class I: No limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
- Class II: Slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
- Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
- Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

5.1.8 **Renal artery evaluation**

Renal artery evaluation results from either computed axial tomography (CT scan), duplex ultrasonography, angiography, or magnetic resonance (MR) angiography will be collected if available.

5.2 Renal Denervation Procedure

The renal denervation procedure should always be done with the aid of fluoroscopy. After confirming subject renal artery anatomy and inclusion and exclusion criteria the site will prepare and perform the renal nerve ablation according to the EnligHTN™ Renal Denervation System Instructions for Use (IFU).

The investigator will select the appropriate basket size of the EnligHTN™ Renal Artery Ablation Catheter (small size for a renal artery diameter between 4mm and 6mm and large size for a renal artery diameter between 5.5mm and 8mm). The EnligHTN™ Renal Artery Ablation 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 EnligHTN™ Renal Artery Ablation 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 lesions are recommended) in the main renal artery. When the ablation procedure is completed in this main renal artery, the EnligHTN™ Renal Artery Ablation Catheter will be withdrawn from the artery with the basket fully closed. Images of the renal artery using a 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 contra-lateral main renal artery. When the ablation procedure for the contra-lateral main renal artery is also completed, the EnligHTN™ Renal Artery Ablation Catheter will be withdrawn from the artery with the basket fully closed and the catheter will be visually inspected and flushed with heparinized saline. Finally, the sheath will be removed according to the institution’s standard of care.

Procedural data collected will include but is not limited to:

- EnligHTN™ Renal Denervation System device information
- Guiding catheter used – manufacturer
- Number of arteries ablated
- Number of ablations performed
- Device settings
- Procedure time
- Ablation time
- Fluoroscopy time
- Volume of contrast media
- Adverse events (check if any adverse events or adverse device effects occurred since enrollment of the patient into the study, and document the event in the hospital records and report the adverse event according to specifications in section 6.7.8.)

5.3 Discharge

Discharge is expected to occur within 72 hours post procedure. The following information will be collected:

- Weight (as part of the Physical assessment)
- Office Blood Pressure (as the average of three measurements)
- Anti-hypertensive medication

- Adverse events (check if any adverse events or adverse device effects occurred since enrollment of the patient into the study, and document the event in the hospital records and report the adverse event according to specifications in section 6.7.8.)

5.4 Follow-up visits

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

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

5.4.1 **Medications**

Anti-hypertensive medication will be collected at each follow-up visit.

5.4.2 **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[49, 50].

5.4.3 **Ambulatory Blood Pressure**

When performed per standard of care, daytime mean ABP, night time mean ABP and 24 hour average ABP values will be collected.

5.4.4 **Blood and Urine Analysis**

Blood and urine samples will be drawn and analyzed, and the following results will be collected at both the 6 months and 12 months follow-up visit:

- Serum Creatinine
- eGFR
- Urine albumin to creatinine ratio (if available per standard of care)

5.4.5 **NYHA Assessment**

NYHA Assessment[53] will be evaluated at the 1 month, 6 months and 12 months follow-up visits and will be classified as the following:

- Class I: No limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
- Class II: Slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
- Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
- Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

5.4.6 **Renal artery evaluation**

At 6 months, renal artery evaluation results from either computed axial tomography (CT scan), duplex ultrasonography, angiography, or magnetic resonance (MR) angiography will be collected if available.

5.4.7 **Adverse Events**
Confirm if any adverse events or adverse device effects occurred since the last visit and document in the hospital records. Report the adverse events according to specifications in section 6.7.8.

5.5 Clinical Investigation Termination

Each subject will be followed for 1 year 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. A Clinical investigation Termination CRF should be completed by the site and provided to the Sponsor.

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, the 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.

5.6 Description of activities performed by Sponsor Representatives

Trained sponsor personnel may perform certain activities to ensure compliance to the investigational plan and may provide technical expertise.

Sponsor personnel will not:

- Perform the informed consent process
- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect clinical investigational data or complete study documentation

5.7 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.

6 Clinical Investigation Conduct

6.1 Ethics Committee

A duly constituted EC representing the prospective study site must review and approve the subject informed consent and research authorization document, the Clinical Investigation Plan, 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 Patient Informed Consent form
- the approved version of any other submitted document (e.g. 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.

6.2 Ethical Basis

This clinical investigation will be performed in accordance with the most current versions of the World Medical Association Declaration of Helsinki and any applicable regional and national regulations. 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.

6.3 Insurance

As sponsor, SJM has taken up general liability insurance in accordance with the requirements of the applicable local laws. If required, additional subject coverage or an investigation specific insurance shall be provided by the Sponsor as well.

6.4 Statements of Compliance

ISO14155 shall be used as a guideline with following exceptions:

- Limited AE reporting -> refer to section 6.7.8
- Device Deficiencies
- Device Accountability

The investigator shall not start enrolling subjects or requesting informed consent prior to obtaining Ethics Committee approval and Competent Authority approval, if applicable, 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.

6.5 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. 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 affect 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.

6.5.1 **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:

- Contacting the investigator by telephone
- Contacting the investigator in writing
- Visiting the investigator
- Retraining of the investigator
- Site "for-cause" audit
- Implementation of corrective action preventive action plan

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.

6.6 Informed Consent Process

6.6.1 **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 and the study center's EC. Prior to the patient signing the PIC, 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 personally 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.

6.7 Adverse Event, Adverse Device Effect

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

6.7.1 **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,
    - Desinfection of medical devices

- 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

6.7.2 **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.

6.7.3 **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.

6.7.4 **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.

6.7.5 **Serious Adverse Device Effect (SADE)**
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

6.7.6 **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.

6.7.7 **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.

6.7.8 **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 form). 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 Adverse Events and all Adverse Device Effects (regardless of severity) are to be documented and reported to the sponsor immediately and 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 or is directly linked to 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 in the eCRF. All unresolved AEs should be followed by the investigator until resolution is reached.

Note: Refer to Table 1 ‘Data Collection’ and Appendix D ‘Data Collection Method’.
In case of EDC failure, notify Sponsor via fax (+800 2546 2546) or e-mail (AdverseEvent@sjm.com).

6.8 Subject Death

6.8.1 **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 D ‘Data Collection Method’
In case of EDC failure, notify Sponsor via fax (+800 2546 2546) or e-mail (AdverseEvent@sjm.com).

Subject Death is the outcome of a serious adverse event (SAE). Death can therefore be 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. Prior

to sending such documentation, personal identifiers will be redacted and replaced by the study-specific subject ID.

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.

6.9 Document and data control

6.9.1 **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.

6.9.2 **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 and signed 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.

6.9.3 **Review of data**

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

The following activities will occur:

- 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.

6.10 Monitoring

Risk-based 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.

6.10.1 **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.

6.10.2 **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.

6.11 Competent Authority (CA) Inspections

The investigator and/or delegate should contact SJM immediately upon notification of a CA inspection at the site. A clinical representative 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.

6.12 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.

At termination, the investigator shall return all documents to the sponsor, and notify the Ethics Committee and the Competent Authority (where applicable). Follow-up for all enrolled subjects will be continued as per standard of care.

6.12.1 **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.

6.12.2 **Investigation Conclusion**

The investigation will be concluded when:

- A Close Out visit has been performed at each participating site AND
- The final report has been provided by the sponsor.

7 Risks and Benefits of the clinical investigation

7.1 Anticipated clinical benefits

It is expected that subjects undergoing a renal denervation procedure with the EnligHTN Renal Denervation System will experience additional and sustainable blood pressure lowering effects compared to drug treatment alone.
The information collected in this clinical investigation will be added to the current knowledge and understanding of treatment options for patients with uncontrolled hypertension.

7.2 Anticipated Adverse Events and Adverse Device Effects

Adverse events potentially associated with the use of the EnligHTN Renal Denervation System and their potential complications are documented in the Instructions for Use (IFU) which is available upon request.

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

No additional risks above those known for the device are to be expected in this observational study. Following efforts to minimize risks will be taken:

- Regular clinical investigation monitoring visits with risk-based monitoring of collected patient data across all centers.
- Conduction of the clinical investigation in accordance with the Clinical Investigational Plan (CIP), all applicable laws and regulations 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 the EnligHTN Renal Denervation procedure.

7.4 Risk-to-benefit rationale

The risks associated with the EnligHTN Renal System are comparable to those associated with the use of other currently available renal denervation systems. Patients participating in this clinical investigation are indicated for a renal denervation procedure as part of their standard medical management and are subject to the risks associated with these devices. It is considered that renal denervation offers a better long-term prognosis which should fairly outweigh the potential risk associated with such procedure.

8 Statistical considerations

8.1 Study design

This is a post market, prospective, observational study of the EnligHTN™ Renal Denervation System. Approximately 500 subjects with uncontrolled hypertension will undergo renal artery ablation at approximately 50 investigational sites located in Europe and the Middle-East and will be followed up to 1 year post procedure.

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

8.2 Sample size estimation

The sample size estimation is based on the primary objective of this study. The aim is to define a precise two sided 95% confidence interval with a half width of 2.35mmHg for the mean reduction of office SBP at 6 Months. Using estimates from the EnligHTN 1 study, the mean ±SD for reduction of office SBP at 6 Months was -26 ±24.7mmHg. In order to achieve the desired level of precision a total of 425 patients is needed. Assuming a 15% attrition rate the study will aim to enroll approximately 500 patients.

8.3 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 form, and had the EnligHTN™ Renal Denervation System enter his/her body. The sample size of 500 subjects refers to 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 been 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 who withdraw from the investigation will not be replaced in any analysis population.

8.4 Data Analysis and Reporting

Data analysis will be performed across all subjects, 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 (number of observations, mean, standard deviation, minimum and maximum values).
Continuous primary and secondary outcomes between time points will be compared as follows: normality of data will be verified with the use of box plots and Kolmogorov-Smirnov normality tests. For normally distributed data, comparisons will be performed using paired t-tests. In cases

where the data is not normally distributed, the non parametric Wilcoxon-Signed-Rank test will be used to analyze the data. Results will be expressed in terms of p-values.
Categorical data will be summarized using frequencies and percentages.

8.4.1 **Primary objective analysis**

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

8.4.2 **Secondary objectives analysis**

Acute (30 days post procedure)

- Safety
  The percentage of subjects with peri-procedural events within 30 days post procedure will be computed as follows:

$$\frac{Number\ of\ subjects\ with\ peri\ procedural\ events\ within\ 30\ days\ post\ procedure}{Number\ of\ subjects\ that\ underwent\ the\ procedure} * 100$$

- Performance
  The mean reduction in office Systolic and Diastolic Blood Pressure at 1 month and the mean reduction in ambulatory Systolic and Diastolic Blood Pressure at 1 month will be calculated in a similar way as described for the primary objective (Section 8.4.1).The percentage of subjects achieving office Systolic Blood Pressure < 140 mmHg at 1 month will be computed as follows:

$$\frac{Number\ of\ subjects\ achieving\ office\ SBP < 140\ at\ 1\ month}{Number\ of\ subjects\ with\ data\ available\ at\ 1\ month} * 100$$

Mid to long term (6 and 12 months)

- Safety
  Renal function change based on eGFR will be summarized by:

  1. Computing the change of the eGFR at 6 and 12 months, compared to baseline for each patient with data available at both time points.
  2. Calculating the mean and standard deviation of the eGFR change at those intervals

  Assessment of renovascular safety as measured by occurrence of new renal artery stenosis (> 50%) and aneurysm at the site of ablation per Renal Artery Imaging will be summarized at 6 months as a percentage of subjects who have stenosis (> 50 %) or aneurysm.

- Performance

The mean reduction in office Systolic Blood Pressure at 12 months, the mean reduction in office Diastolic Blood Pressure at 6 and 12 months and the mean reduction in ambulatory Systolic and Diastolic Blood Pressure at 6 and 12 months post denervation will be calculated in a similar way as described for the primary objective (Section 8.4.1).
Percentage of subjects achieving office Systolic Blood Pressure < 140 mmHg at 6 and at 12 month will be computed as follows:

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

$$\frac{Number\ of\ subjects\ achieving\ office\ SBP < 140\ at\ 12\ months}{Number\ of\ subjects\ with\ data\ available\ at\ 12\ months} * 100$$

8.4.3 **Other Analyses**

Summary statistics for medications being used by subjects and changes to them will be presented for each follow-up visit.

In addition, subgroup analyses may be performed as needed, e.g.:

- 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)
- based on the number of ablation points performed
- by the subject's primary disease conditions.

Ad hoc analyses may be performed as needed. Analysis may be performed based on As Treated population as deemed appropriate. 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.

8.4.4 **Analysis Software**

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

9 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.

9.1 Data Management Plan

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

The Data Management Plan (DMP) 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) when applicable 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.

9.2 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.

9.3 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, which will be kept on the site, the available demographic and medical information of a subject shall be documented, in particular the following:

Name	Date of Birth	Weight
Gender	Height	Concomitant Medication
Subject History	Concomitant diseases	Scheduled follow ups
PIC process	Date of PIC	Observed AEs
CIP required examinations	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 be part of the subject's source data.

9.4 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 SJM International, Inc. and its affiliates, 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:

- Monitoring the accuracy and completeness of the study
- Performing scientific analysis and developing the medical product
- And/or obtaining 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, address, and

hospital number) and only be identifiable by a study-specific subject 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, the European Economic Area 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.

10 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.

11 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 the Coordinating Investigators.

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. This information will be incorporated when an amendment occurs.

12 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 such a Clinical Trial Agreement.

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

13 Investigation Organization

13.1 Investigation Management / Sponsor

The organization, which takes responsibility for the initiation and/or implementation and coordination for the investigation is SJM International, Inc., with offices located at:

SJM International, Inc.
Corporate Village, Building Figueras
Da Vincilaan 11, Box F1
B-1935 Zaventem
Belgium
Tel: +32 2 774 69 37
Fax: +32 2 774 69 46

As defined in the Power of Attorney (PoA), SJM International will delegate responsibilities to the local SJM clinical entity in each participating country or region.

Sponsor Responsibilities
Sponsor's responsibilities are in accordance with applicable guidelines, covering the design, overall conduct, analysis and reporting of the results of the study. This includes but is not limited to the following activities:

- Perform those actions necessary to protect the rights of subjects and the scientific credibility of the manner in which this study is conducted;
- Select 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;
- Develop the study database;
- Train 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 (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);
- Review the investigator´s assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device;
- Report or ensure reporting of all serious adverse events to the EC by the Principal Investigator(s), if required by the EC, by national regulations or by the CIP;
- Report all serious adverse events to regulatory authorities within the required time period, if required by national regulations or by the CIP;
- Maintain an updated list of principal investigators, investigational sites and institutions. This list shall be available upon request;
- Design revision controlled CRFs and Patient Information Sheet / Patient Informed Consent form templates;

- Obtain signed Study Agreements and completed Investigator Financial Disclosure information;
- Collect EC approval letters, including a copy of the approved information sheet and consent forms;
- Archive all correspondences relating to the conduct of this study between SJM and the study site, ECs, and Study Monitors;
- Collect CVs and professional licenses for all study personnel, if applicable;
- Obtain protocol/device related training records for all applicable study personnel;
- Collect site personnel signatures and documentation of the Investigator's delegation of study related responsibilities;
- Collect a list of EC voting members;
- Provide insurance certificates.

13.2 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. Provide signed and dated CVs (for all members of the investigational team) and other relevant documentation,
3. Be experienced in the field of application and have documented training of investigational device use under evaluation,
4. Disclose potential conflicts of interest, including financial disclosure,
5. Be knowledgeable in 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 well 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 Clinical 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;
- Assuring strict adherence to the CIP testing requirements to provide for optimal safety and efficacious use of the device under clinical investigation;
- Performing adequate safety reporting (including complete AE source documentation (e.g. to allow for accurate adjudication of events by the sponsor);
- 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;
- Signing off the signature page for each final version of the clinical investigation plan (including 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 Log (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 (CCI)
In addition to the responsibilities of the Principal Investigators, the Clinical Coordinating Investigator will:

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

The following investigator has been appointed by the Sponsor as the Clinical Coordinating Investigator:

Dr. José Diaz
Hospital Juan Ramon Jimenez
Ronda Norte
21005 Huelva
Spain
Tel: +34 616 67 6095

13.3 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 Clinical Research Organization 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.

13.3.1 Power of Attorney (POA)

The POA delegates sponsor's responsibility for specified tasks to the country entities, divisions or designees, 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: Abbreviations

Abbreviation	Term
ABP	Ambulatory Blood Pressure
ACE-I	Angiotensin Converting Enzyme Inhibitor
ADE	Adverse Device Effect
AE	Adverse Event
ARB	Angiotensin II Receptor Blocker
ASADE	Anticipated Serious Adverse Device Effect
BP	Blood Pressure
CA	Competent Authority
CCI	Clinical Coordinating Investigator
CIP	Clinical Investigational Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CPRB	Clinical Project Review Board
CT	Computed axial Tomography
CV	Curriculum vitae
DCC	Data Cleaning Convention
DMP	Data Management Plan
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EEA	European Economic Area
eGFR	estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions For Use
Ir	Iridium
ISB	Investigator Site Binder
ISO	International Organization for Standardization
MDRD	Modification of Diet in Renal Disease
MP	Monitoring Plan
MR	Magnetic Resonance
NYHA	New York Heart Association
PI	Principal Investigator
PIS	Patient Information Sheet
PIC	Patient Informed Consent
POA	Power of Attorney
PTFE	Polytetrafluoroethylene
Pt	Platinum
RDC	Remote Data Capture
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SJM	St. Jude Medical
UADE	Unanticipated Adverse Device Effect

USA	United States of America
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

Appendix B: 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
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. 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 be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. 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."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. 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 proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must 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.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this 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.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. 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.
22. The design and performance of each research study involving human subjects must be clearly described and justified 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, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. 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 amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, 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, post-study provisions 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. All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must 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 must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised 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 group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent 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 authorised representative. The potential subject's dissent should be respected.
30. 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 group. In such circumstances the physician must seek informed consent from the legally authorised 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 must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their 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 adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention

will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers 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. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

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

Appendix C: Device Manual

The EnligHTN RF ablation generator, the EnligHTN Renal Artery Ablation Catheter and the EnligHTN Guiding cathether (optional) will be used according to the Instructions For Use.

Appendix D: Data Collection Method

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 1:1.
Source documents include all original records from which CRFs derive their data. All documentation pertaining to clinical assessments and medical evaluations should be signed and dated by the appropriate clinical personnel.

Electronic Data Capture (EDC) will be used for this investigation, therefore, please find below instructions on how to access and use the eCRF application.

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.

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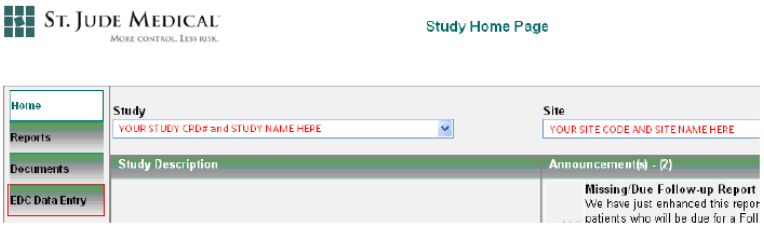
RDC OnSite Tip Card

- **For protocol related questions please contact your FCE or project team.**
- **For any technical issues with RDC OnSite please call our toll free help line at 866-593-2910 or send an e-mail to EDC@sjm.com.**

Logging Into RDC OnSite:

1. Click on the SJM Portal link provided to you by email. Enter your username and password. Pressing "Enter" will take you to the Study Site Portal. Click on the link to access the SJM Study Site Portal, where you can access information regarding your Study/Site.
2. Select the appropriate Study and Site Name from the dropdown menus. Pressing "Go" takes you to the Portal Study Home Page. **NOTE:** Applies to users with multiple SJM EDC studies. Users with access to a single EDC study are taken directly to the Portal Study Home Page upon entry.
3. Locate the 'EDC Data Entry' hyperlink on the left side. Clicking this hyperlink launches a new web browser opened to the RDC OnSite login screen.
4. Enter your Username and password again. You will be taken to the RDC OnSite Home Page where you can begin working with your study.

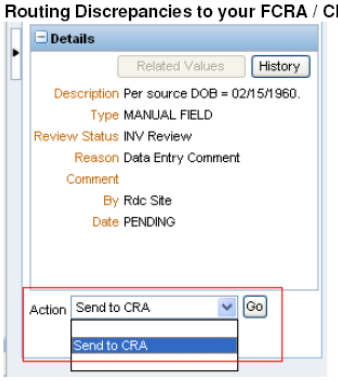
NOTE: Only one RDC OnSite session window can be open at a time. If you try to open additional sessions you will be logged out of any open sessions.



Opening a Subject Casebook / Case Report Form (CRF):

1. From the RDC OnSite Home Page mark the checkbox under the "Select" column for each subject casebook to be viewed.
2. Select from the "Select Patients and…" dropdown menu field the "Open Patient Casebook" option and press "Go". You will be taken to the Casebook Page, where each selected subject casebook will be listed in table format.
3. From the Casebook Page click a CRF icon to open the CRF. A new web browser window will open known as the **Data Entry Window (DEW)**.
4. If required, change the Study Visit by selecting it through the "Visit" dropdown menu.

Routing Discrepancies to your FCRA / CRA – DEW Navigator Pane:

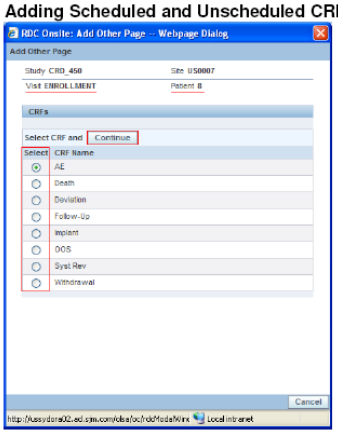


Route Discrepancies to your FCRA / CRA for resolution when:

- Data changes for Automated Edit Checks still violate Edit Check Rules; and
- Addressing manually entered Discrepancies.

1. Expand the Navigator Pane by clicking on the arrow on the right-edge of the DEW.
2. Click on an Active Discrepancy within the List sub-pane.
3. Review the Discrepancy Description within the Details sub-pane to assess the appropriate action. Change data on the CRF if required.
4. At the bottom of the Navigator Pane locate the "Action" dropdown menu field and select the "Send to CRA" option. Press "Go".
5. In the Discrepancy Action – Send to CRA dialogue window enter a Comment and press "OK" to route the Discrepancy to the FCRA / CRA.
6. After all CRF activities are completed save your changes by pressing the "Save" icon. Click the DEW Close icon "X" to return to the Casebook Page.

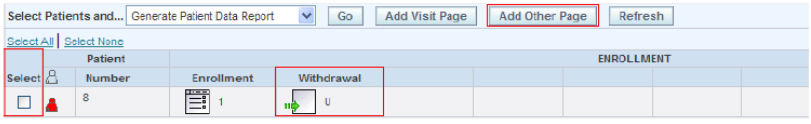
Adding Scheduled and Unscheduled CRFs to a Study Visit – Casebook Page:



- **Add Visit Page** – Adds CRFs scheduled for the Study Visit (eg, another Implant form).
- **Add Other Page** – Adds CRFs not scheduled for the Study Visit (eg, an AE form to a 6-Month visit).

1. Mark the checkbox for the Subject casebook you want to add the CRF to and press either the "Add Visit Page" or "Add Other Page" button to open the appropriate dialogue window.
2. In the dialogue window select the radio button for the CRF to be added. Press the "Continue" button.
3. In the dialogue window the CRF sub-visit field will automatically be set to the next available number, therefore, you won't need to change it (for Add Visit Page only). Press the "Apply" button to continue. The CRF icon will appear in the Study Visit.
4. **If the CRF was added in error** and no data was saved onto the form, press the "Refresh" button and the CRF will be removed from the Study Visit.

NOTE: Add Visit Page can be used only after data entry is started on at least one scheduled CRF in that Study Visit.



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Summary of Casebook Status Icons – Home Page

	No Data Entry is started.
	At least some Data Entry is saved. No Open Discrepancies.
	At least some Data Entry is saved. Active Discrepancy present on at least one CRF requiring current user's attention. May also include Other Discrepancies.
	At least some Data Entry is saved. Other Discrepancy present on at least one CRF requiring current user's attention. No Active Discrepancies present.

Summary of CRF Status Icons – Casebook Page

	CRF not started. Data entry is expected.
	Save Incomplete CRF – The CRF was started and only the Visit Header Date was completed.
	Save Incomplete CRF – Data Entry is incomplete. User is not done inputting all the data, and will finish at a later time.
	Save Complete CRF – Data Entry is complete. User has met all the requirements for the form, and the responses are considered complete. Automated Discrepancy Edit Checks are activated. CRF has no open issues.
	Save Complete CRF – Data Entry is complete. CRF contains Other Discrepancies that another user group must address.
	Save Complete CRF – Data Entry is complete. CRF contains Active Discrepancies that the current user group must address.
	*Approved CRF – CRF Data responses have been approved by an investigator. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	*CRF requires Re-Approval – Looped arrow next to signature indicates Data, an Investigator Comment, and/or Discrepancy was updated since the CRF was Approved. (If Open Discrepancies are present, the icon would also be red or yellow.)
	Verified CRF – CRF Data responses are verified against source documents. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Active Discrepancies present.
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Other Discrepancies present.
	*CRF is Verified and Approved – CRF Data responses are verified against source documents by the FCRA / CRA, and the Data responses approved by the Principal Investigator.
	CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Active Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Other Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF at Pass 2 Complete. This icon indicates Data Entry was completed by the sponsor in-house using data submitted on paper CRFs.

*APPROVAL FEATURE CURRENTLY AVAILABLE TO INVESTIGATORS FOR THE DEATH CRF ONLY.

Summary of Discrepancy Status Icons – Data Entry Window (DEW) Navigator Pane

	Active Discrepancy that the current user group must address.
	Other Discrepancy that another user group must address.
	Resolved Discrepancy requiring no further action by any user group.

NOTE: Obsolete Discrepancies due to Data updates or Validation Procedure / Automated Edit Check updates will be removed from the List sub-pane.

Summary of Data Entry Window (DEW) Toolbar Icons

	Add Discrepancy		Delete Row		Approval History		*Print		First/Previous Page		Close
	Investigator Comment		Verification History		Approval		Save		Next/Last Page		

*DO NOT USE THESE TOOLBAR FUNCTIONS

Helpful Hints:

1. **CRF Deletions** – If a CRF with saved data requires deletion notify your SJM contact, providing information about the form.
2. **Refresh** – Press the "Refresh" button to refresh RDC OnSite with current information (statuses, etc.)
3. **Printing a Subject Casebook / CRF** – Go to the RDC OnSite Report Page to print a Patient Data Report. Report types include casebooks with saved Subject data and blank Subject casebooks.
4. **Logout** – Use the web browser close icon "X" to exit. To re-enter, navigate through the SJM Portal.

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