

# Protocol

## **Feasibility study of a randomised controlled trial investigating renal denervation as a possible treatment option in patients with Loin Pain Hematuria Syndrome**

### **Overview**

---

Loin Pain Hematuria Syndrome (LPHS) is a rare and poorly understood clinical condition characterized by severe, unilateral or bilateral loin pain localized to the kidney in the absence of identifiable urinary tract disease. The presence of pain-carrying fibers in the renal arterial adventitia presents an opportunity to interrupt the pathways by using radiofrequency nerve ablation as an alternative to chronic pain medication. Recent case reports and small case series from our group and others have shown renal denervation to be a potent therapeutic target for patients with LPHS.

The present study is a prospective, double-blinded, parallel group, sham-controlled, partial crossover, randomized feasibility trial. This feasibility trial is designed with an aim to determine the viability of the proposed main trial initiative and to provide framework and direction for the larger randomized control trial. This study is intended to supplement a larger clinical trial to assess both statistical and clinical significance of renal denervation treatment in LPHS patients. Renal denervation will be performed using the Symplicity Spyral™ multi electrode renal denervation system - a percutaneous system that delivers radiofrequency (RF) energy through the luminal surface of the renal artery. This study will enrol 10 LPHS patients and will be conducted at a single site i.e. Regina General Hospital.

**Study Hypothesis:** In the present study we hypothesise that the recruitment, intervention, measurement and trial procedures will be feasible and acceptable, thus allowing us to proceed with a full randomised control trial

**Objectives:** The objectives of the study are:

- a.) Assessing our recruitment capability**
- b.) Evaluation of Data Collection Procedures and Outcome Measures**
- c.) Assessing acceptability of intervention and study procedures**
- d.) Evaluation of resources and ability to manage the Study and Intervention**
- e.) Effectiveness of intervention**

### **Long-Term Objectives**

We are optimistic that renal denervation (RDN) will reduce self-reported pain in patients diagnosed with LPHS and that an adequately-powered randomised control trial (RCT) is feasible. We hope that RDN will eventually be considered a mainstream treatment for patients with LPHS.

Our primary clinical hypothesis or **secondary outcome** is expected as a 30% reduction in subjective pain ratings using a 79-point (0-78) Mc Gill pain score and the Brief Pain Inventory Score in LPHS patients as compared to sham treated patients, at 6 weeks post treatment, which will be maintained at 3 and 6 months post-procedure.

## Background Information

---

Loin Pain Hematuria Syndrome (LPHS) is a rare clinical disorder with a reported prevalence of 0.012%<sup>1</sup> and typically impacts younger women. Since the initial description in 1963<sup>2</sup>, it remains a poorly understood clinical condition characterized by severe, unilateral or bilateral loin pain localized to the kidney but in the absence of identifiable urinary tract disease. Hematuria can be either microscopic or macroscopic, and the renal abnormalities responsible for both pain and hematuria are unexplained.<sup>1</sup>

It is likely that multiple as yet unrecognized stimuli are responsible for the agonizing and unrelenting pain. Nociceptive fibers are transmitted in afferent Aδ and C fibers from the kidney, coursing through the periarterial nerves, ascending by way of renal and intermesenteric plexi to the lowest splanchnic nerve and passing via the dorsal roots of T11 through L1 to the spinothalamic tracts.<sup>2,3</sup> The predominant clinical feature of LPHS is intense unilateral or bilateral loin pain which may be intermittent or constant dull ache with intermittent exacerbations. While spontaneous disappearance of the pain has been reported, the natural history is of recurrent episodes of debilitating pain refractory to conventional pain medications. Six decades after its initial description, there is no consensus on validated diagnostic criteria or optimal treatment strategies for LPHS. The diagnosis continues to be one of exclusion.

Pain is experienced unilaterally or bilaterally along the flank (costovertebral angle) and may be described as a “deep pain” which is intensified by a “gentle punch” and must be recurrent for six months or more in order to meet diagnostic criteria.<sup>6</sup> Pain should also be sufficiently severe to prompt the patient’s primary care physician or urologist to prescribe or consider narcotic therapy. For patients identified as presenting with LPHS, hematuria is defined as greater than five red blood cells (RBC)/high-power field (HPF).<sup>6</sup> If there is a history of overt hematuria, it must be accompanied by

worsening pain; however, severe pain could be present without overt hematuria <sup>6</sup>. If nephrolithiasis had occurred in the past, then a recent imaging study should rule out obstruction of the urinary tract. The disease imposes a significant health and economic impact in terms of loss of productivity and quality of life in a young population as they are shuffled between numerous health care providers in search of a diagnosis<sup>7</sup>. Multiple visits to the emergency rooms add to the significant burden of investigations and consultations. The debilitating pain leads to increased absenteeism, fragments interpersonal relationships, increases the risk of mood disorders and severely interrupts the quality of life.

Adequate pain relief remains the goal but is rarely achieved. Inter disciplinary pain management clinics focussing on drugs (opioids, non-opioid analgesics, antiepileptic drugs, antidepressants, and muscle relaxants) and physical and behavioural medicine interventions have been disappointing with more than half of the patients experiencing no improvement in pain<sup>8,9</sup>. Additional pharmacotherapeutic therapies including angiotensin-converting enzyme (ACE) inhibitors, inhibitors of complement activation, and 5-hydroxy tryptamine (5HT3) antagonists have been ineffective<sup>8,10</sup>. Innovative attempts to modulate the nerve pathways (transcutaneous electrical nerve stimulation, <sup>10</sup> dorsal rhizotomy, <sup>10</sup> capsaicin instillation in the renal pelvis,<sup>11,12</sup> renal capsulectomy<sup>13</sup>, and thoracolumbar sympathectomy<sup>14</sup>) to achieve pain control have been associated with variable outcomes.

## **Therapeutic Renal Denervation**

---

Renal denervation uses radiofrequency energy to selectively sever renal nerves that travel to and from the kidney to the central nervous system. The concept of therapeutic renal denervation in LPHS is not new. Laparoscopic renal denervation and autotransplantation as means of interrupting the pathways have been associated with better pain relief in LPHS.

Radiofrequency nerve ablation is a minimally invasive alternative to opiate therapy, autotransplantation and nephrectomy in LPHS. In our previous exploratory pre/post single centre studies, we showed promising results with regards to pain relief, mood, disability and quality of life post procedure. As our initial study was neither blinded nor randomized, improvements in pain and quality of life scores owing to a placebo effect cannot be ruled out <sup>15, 16</sup>; hence, to preclude any cause-effect relation between treatment and outcome, selection-bias, influences we intend to conduct a RCT with a sham arm. The present study is designed to assess the feasibility of conducting a large scale randomised control trial. Given the magnitude of change observed in our previous study (Figure 1),

however, it seems unlikely that these improvements would be entirely attributable to participants' expectations regarding the efficacy of the procedure.

## **Device**

---

Symplcity Spyral™ multi-electrode renal denervation system including Symplcity Spyral™ multi-electrode catheter (Symplcity Spyral catheter, Medtronic) and associated Symplcity G3™ renal denervation radiofrequency generator (Symplcity G3 generator, Medtronic) will be used in this study. For this study we require 10 Symplcity Spyral™ multi-electrode renal denervation systems. The Symplcity Spyral™ multi-electrode renal denervation catheter is intended to deliver low-level radio frequency (RF) energy through the wall of the renal artery to denervate the human kidney. The Symplcity Spyral™ multi-electrode is a redesigned catheter with reduced procedural time, enhanced ease of use and improved safety and efficacy measures.

The distal end of the Symplcity Spyral catheter consists of a spiral shaped, self-expanding nitinol elements onto which four electrodes are mounted. When deployed, the electrodes are at 90 degrees orthogonally from each other to cover all four quadrants of the artery's circumference in a helical fashion. The distal end of the catheter is designed to provide uniform electrode-arterial wall contact in vessels ranging in diameter between 3 mm and 8 mm. Only one catheter is needed to complete a bilateral denervation procedure as it performs in a wide range of anatomies. The four electrodes simultaneously deliver RF energy for 60 seconds. Using standard interventional techniques, the Symplcity Spyral™ catheter will be placed in the renal artery, radiofrequency energy ablations of 60-second durations will be delivered through the catheter's electrodes to the arterial wall and surrounding tissue where sympathetic nerves reside.

## **Research Design and Methods**

---

### **Overview**

This study is a double-blinded, parallel group, sham-controlled, randomized control, partial crossover feasibility trial. This feasibility trial is a part of a larger clinical trial to assess both statistical and clinical significance of renal denervation treatment in LPHS. This trial will involve 10 Saskatchewan based patients for whom travel will be covered to and from Regina. These patients will be randomized to either receive the treatment procedure or the sham procedure.

To assess the feasibility measure, the QuinteT recruitment intervention methodology will be utilized, involving a researcher interviewing patients at 6 months after the study (with the inclusion of a satisfaction likert question regarding the study) and interviewing the study personnel throughout the trial.<sup>17</sup> Patient identifiers will be kept anonymous throughout the QuinteT process, and the interviewer will be blind to the treatment allocation of the patient.<sup>18</sup> The feasibility assessments will be reported in accordance with the CONSORT 2010 statement: extension to randomised pilot and feasibility trials guidelines<sup>19</sup>.

### **Study Objective**

This feasibility trial is designed with an aim to determine the viability of proposed main trial initiative and to provide framework and direction for the larger randomised control trial. To do this, we will investigate specific feasibility endpoints:

#### **The specific feasibility objectives of this study are:**

##### **1) Assessing our recruitment capability:**

- Can we recruit appropriate participants?
- How difficult is a large-scale recruitment and retention for LPHS?
- Are the eligibility criteria appropriate?
- How many participants accept the eligibility criteria

##### **2) Evaluation of Data Collection Procedures and Outcome Measures:**

- How appropriate are the data collection procedures in this study?
- Do participants have difficulty completing the measures proposed in this study?
- Does the overall data collection plan involve a reasonable amount of time, or does it create a burden for the participants?

##### **3) Study Procedures:**

- Are the study procedures acceptable to the participants?
- How many participants adhere to the study procedure?
- What is the acceptability of being in control group to the participants?
- Is the intervention suitable for and acceptable to the participants?
- How many participants will crossover to the intervention group after being in control group initially?
- What is probability of unexpected adverse events?

##### **4) Evaluation of resources and ability to manage the Study and Intervention:**

- Do we have enough resource and space to manage the study?

- Are the research investigator and staff capacities, expertise and availability for the planned research activities adequate?
- Evaluate the time to conduct each stage and aspect of the protocol? What are the time frames, and how do they coordinate with other responsibilities?
- **Management of the ethics of the research:**
  - To what extent does staff comply with the approved protocol?
  - How effectively are adverse events during implementation identified, documented, and reported?
  - What happens if a participant experiences a clinical emergency?
- **Effectiveness of Intervention:**
  - Does the intervention show promise of being successful with the intended population?
- ❖ **Effectiveness of intervention will be determined based on following criteria:**
  - Whether participants receiving RDN have  $\geq 30\%$  reduction in pain medication dose (primarily opioids using morphine equivalent) as compared to sham treatment group at 3 and 6 months post-intervention, reported using a daily pain diary (attached).
  - Whether participants receiving RDN have significant reduction in self-reported disability (Oswestry Disability Index) at 6 weeks, 3 and 6 months as compared to sham treatment group.
  - Whether participants receiving RDN (have significantly improved Quality of Life (EQ5D, SF-36 Questionnaire) at 6 weeks, 3 and 6 months as compared to sham treatment group.
  - Whether participants receiving RDN have significantly improved mood (CES-D Short Form) at 6 weeks, 3 and 6 months as compared to sham treatment group.

### **Study Population:**

This study will recruit 10 LPHS patients. Once a potential participant has been identified, the study will be explained for consideration. The potential participant will be given adequate time to carefully consider participation; this may include taking an unsigned copy home to discuss participation with family or friends before making a decision. If the subject agrees to participate, written informed consent will be obtained. Once a participant has consented to the trial they will undergo initial screening to ensure that they meet all of the eligibility criteria. The initial screening will be done on the basis of inclusion and exclusion criteria for participation in this study (except renal angiogram). The final step of screening process is a renal angiogram. LPHS patients who will meet all criteria after the initial screening period will undergo a renal artery angiogram to evaluate renal artery anatomy. Only subjects with eligible renal artery anatomy (between 3 mm and 8 mm) will be randomized. If the

renal angiogram shows that renal artery anatomy is not eligible for the study, participant will be excluded from the study.

### **Selection Criteria**

Participants will be selected based on the following inclusion and exclusion criteria.

#### **Inclusion/ Exclusion Criteria**

##### **Inclusion criteria for participating in the study are:**

- $\geq 18$  years of age
- Diagnosed with loin pain hematuria syndrome by a nephrologist, in consultation with a urologist.
- Current use of prescription pain medication for LPHS treatment.
- Arteries with a diameter between 3 mm and 8 mm.

##### **Exclusion criteria for patients to be screened out of the study are:**

- History of kidney auto transplantation
- Estimated glomerular filtration rate (eGFR)  $<45$  mL/min/1.73m<sup>2</sup>
- Pregnant or nursing
- Need chronic oxygen support or mechanical ventilation via tracheostomy continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP)
- Renovascular abnormalities
- Prior renal angioplasty, indwelling renal stents and/or aortic stent grafts
- Evidence of a somatoform disorder as per the SCID-5
- Unavailable to travel to Regina, SK one day prior to the procedure to meet with the Principal Investigator and study coordinator

### **Trial Interventions**

Renal angiography will be performed to confirm the suitability of renal artery anatomy for renal denervation therapy. If suitability criteria are met, the participant will then be randomized for a sham procedure or a renal denervation procedure by manager of the radiology suite, Regina using a computer program. Participants will be randomly allocated to one of two treatment arms: 1) renal denervation (treatment group) or 2) sham treatment (control group) immediately following the renal angiogram. All eligible participants will have an equal chance to be assigned to either treatment or control group with a 1:1 treatment allocation design being used. Participants will be given general anesthesia, thus they will be blinded to their randomised group assignment; they will not know the

difference between renal angiography procedure alone or renal angiography plus renal denervation procedure. After the procedure, the participants will be sent to the recovery room and the nursing team caring for the patient will be blinded to the procedure. The radiological aspect (sham or procedure) will not be entered on the hospital electronic medical rounds/ PACS. If the angiographic information is needed by other health care professional for a clinical event then it will be released upon request by the Interventional Radiologist.

**Treatment Group:** Participants remain blinded and are immediately treated with the renal denervation procedure.

**Sham Group:** Participants remain blinded and remain in the procedure table for at least 20 minutes prior to introducer sheath removal.

The clinical staff (Nephrologist and Nurse Practitioner) and the study coordinator will be blinded to the treatment allocation. Only the interventional radiologist and his/her designated study staff will not be blinded to a participant's randomization group. The radiologist will not be involved with participants follow up following the procedure. This way, the clinical follow-up will not be affected by clinician or participant knowledge of specific treatment. Unblinding will occur after the six-month follow-up assessment. The participant's will be told the type of treatment received and, if they were allocated to the sham arm, they will undergo the RDN procedure. The participant's treatment allocation will not be revealed until after the six month follow-up period is complete. After the initial 6-month follow-up period is over, the participants who were in sham group will undergo the experimental treatment.

### **Renal Denervation Procedure**

---

Renal denervation (RDN) uses radiofrequency energy to selectively sever renal nerves that travel to and from the kidney to the central nervous system. The procedure involves radiofrequency ablation to both the renal arteries. Symplicity Spyral™ multi-electrode renal denervation catheter (Symplicity Spyral catheter) and associated Symplicity G3™ renal denervation radiofrequency generator (Symplicity G3 generator) (both Medtronic) will be used in this study. The latest generation Symplicity Spyral catheter device features four electrodes configured in a helical arrangement that can simultaneously ablate in four quadrants of the vessel circumference. The renal denervation procedure will be performed according to the supplied Symplicity™ Catheter Instructions for Use. The procedure will be performed by highly skilled proceduralist with vast previous renal denervation experience.



3000 IU of heparin and 50 mcg of Nitroglycerine will be administered in each renal artery. The Interventional Radiologist will gain percutaneous femoral access to introduce the 7Fr Terumo destination sheath under aseptic technique. 0.36-mm diameter guide wire will be introduced via the arterial puncture. This will be followed by insertion of a 6Fr Symplicity Spyral™ (Medtronic) catheter. Once electrodes are well apposed angiographically and impedance values and tracings are stable, radiofrequency (RF) energy will be delivered to the treatment site. The four electrodes simultaneously deliver RF energy for 60 seconds. Final renal angiogram will be obtained to check the integrity of the renal artery. Closure device will be used for all patients to allow early ambulation.

### **Sham Procedure**

In the control group, the sham procedure will consist of only a renal angiogram. Participants will undergo diagnostic renal angiogram but will not receive any therapeutic endovascular treatment. The diagnostic catheter will be kept *in situ* and dummy radiograph scan will be performed for another 10–15 min before removing the femoral sheath from the sedated patient. Participants will remain on the procedure table for at least 20 min after the angiogram to prevent possible unblinding of randomisation allocation.

### **Risk associated with the procedure**

The primary risks of the procedure are similar to the risks of all diagnostic procedures requiring catheterization of the arteries. The following are possible risks of the catheterization procedure, which includes the renal angiogram (with or without the denervation procedure):

#### **Uncommon < 10%, temporary and not severe unless otherwise indicated**

- Nausea or vomiting
- Complications associated with the use of any pain or anxiety medication during or after the procedure
- Complications at catheter insertion site in the groin
  - Pain
  - Bruising
  - Hematoma (collection of blood outside a blood vessel)

#### **Rare < 1%, temporary and not severe unless otherwise indicated**

- Heart rhythm disturbances, including bradycardia (a slowed heart rate)
- Embolism - Formation and dislodgement of a blood clot or dislodgement of cholesterol/plaque within the blood vessel, which travels downstream into small vessels, blocking blood flow and causing temporary or permanent damage to organs in the body. Clots are known to cause heart

attack, stroke, kidney damage, or threaten circulation to arms or legs and may ultimately lead to incapacitation or death.

- Complications at catheter insertion site in the groin
  - Pseudoaneurysm (injury to the artery wall resulting in a build-up of blood under the skin)
  - AV fistula (an abnormal connection or passageway between an artery and a vein)
- Vascular complications requiring surgery
- Perforation or dissection of a blood vessel, such as the renal artery (unintended puncture through the wall of a blood vessel, such as a renal artery, requiring repair)
- Hypotension (blood pressure too low)
- Hypertension (blood pressure too high)
- Complications associated with the contrast agent used during the procedure, e.g., serious allergic reaction or reduced kidney function.
- Complications associated with medications commonly utilized during the procedure – known risks of medications commonly used during the procedure (e.g., narcotics, anxiolytics, other pain medications, anti-vasospasm agents).

**Very Rare <0.1%**

- Complications at catheter insertion site in the groin
  - Infection (localized redness, heat swelling and pain at the catheter insertion site)
  - Significant bleeding (blood loss from the catheter insertion site requiring surgery or transfusion of 2 or more units of packed red blood cells (PRBCs).
- Retroperitoneal bleeding (bleeding into the retroperitoneal space). Vascular complications requiring surgery – damage to an artery (e.g., femoral) or vein requiring surgical repair.
- Cardiopulmonary arrest
- Death

**There are additional risks that could possibly be associated with the denervation procedure/response to treatment. These complications have not yet been quantified.**

**These potential risks may include:**

- Pain: during or after the procedure that may require treatment with pain medications.
- Damage to one or both kidneys and/or loss of kidney function: perforation of kidney or an occlusion of blood flow to the kidney (e.g., from stenosis or embolism) and/or reduction of glomerular filtration rate. If severe enough, this could require dialysis.

- Renal artery aneurysm: localized weakening and ballooning of the renal artery from the interventional procedure or the delivery of RF energy.
- Renal artery stenosis: narrowing of the renal artery due to the interventional procedure or the delivery of RF energy.
- Arterial spasm or constriction: Acute or chronic narrowing of the renal artery lumen diameter at denervation locations due to arterial muscle contraction, local tissue contraction or local edema.
- Thermal injury to the vasculature or other structure from energy application: damage to an artery, vein or other structure due to the delivery of energy.
- Hypertension: worsening high blood pressure.
- Hypotension: low blood pressure. BP reduction may occur too far and/or too quickly and may cause end organ hypoperfusion.
- Orthostatic hypotension: temporary reduction of blood pressure when going from lying to standing, coupled with symptoms (e.g., dizziness, light headedness).
- Hematuria: blood in urine.
- Proteinuria: elevated levels of protein in urine.
- Toxic reaction: adverse reaction to introduction of foreign body material (e.g., infection, blood disorder, allergy, fever)
- Electrolyte disturbances: an imbalance of the electrolytes (sodium, potassium).
- Skin burn: damage to the skin caused by energy conduction via the ground pad used with the Symplicity System

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

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

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

The participants will be given general anaesthesia. The side effects or risk associated with general anaesthesia are:

- **Common side effects / risk**

- Nausea and Vomiting
- Dizziness
- Temporary confusion
- Shivering
- Bruising or soreness at the injection site
- A sore throat because of the breathing tube

- **Rare side effects/ risk**

- Intraoperative awareness is a rare risk associated with general anaesthesia, affecting 0.1- 0.2% of patients. Intraoperative awareness occurs when a patient becomes conscious during the procedure performed under general anesthesia and subsequently has recall of these events, leading to long lasting significant trauma.
- Death under general anaesthesia is very rare with a frequency of 0.001%.

The study may involve unknown or unforeseen side effects or complications other than those mentioned above. If the above complications occur, they may lead to repeat or prolonged hospitalization, repeat procedures, emergency surgery, other emergency procedures, or, in rare cases, death. Although there are risks associated with participation, there will be a panel of physicians independent of the study, will monitor the safety of the study. They will be overseeing the safety of all study participants.

**Risk Evaluation:**

In this study we will use Symplicity Spyral™ denervation system. The safety, efficacy and performance of renal denervation treatment using Symplicity Spyral™ denervation system has been tested in pre-clinical and clinical studies. The safety and performance of the Symplicity™ multi-electrode radiofrequency renal denervation system was assessed in a prospective, non-randomised, open label, feasibility study. This study confirms the safety of treating patients with uncontrolled hypertension with the Symplicity multi-electrode radiofrequency renal denervation system. Minimal safety complications were reported, none of which was directly related to the delivery of radiofrequency energy (Table 1). In a recent SPYRAL HTN-OFF MED trial using Symplicity Spyral™ catheter, no major procedural or clinical safety events were observed in either the renal

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

Overall safety analysis of renal denervation system has been very positive. Renal denervation trials using first and second generation symplicity catheter from Medtronic have reported no serious procedure-related or device-related complications and occurrence of adverse events. Renal denervation procedure performed using catheters from other companies including St Jude Medical and Boston scientific have reported no serious or life threatening adverse events. Vascular complications seem rare and are not usually irreversible. So far, minor vasospasm of the renal artery post-denervation, small hematomas, pseudo-aneurysms, minor bleeds, and one dissection requiring stenting have been reported. Endothelial injury at the site of ablation lesions seems to be transient and re-endothelization occurs soon enough. Clot formation at ablation sites can be prevented by appropriate antithrombotic and antiplatelet therapy. Renal artery stenosis seems to be a concern, but indeed, only two cases of renal artery stenosis due to renal nerve ablation have been reported so far, while the procedure has been already performed in several thousand patients. No major renal deterioration has been reported so far. In addition we did not identify any complications in our single centre study in 60 patients who underwent the procedure (for hypertension and LPHS) over the last 4 years.

The risk associated with the procedure also depends on the experience of interventionalist carrying out the intervention. In this study renal denervation procedure will be performed by an experienced and trained interventional radiologist who has performed RDN in close to 60 patients (for loin pain and hypertension). His clinical experience with the procedure and the skill that he has gained will be helpful in minimizing the potential risks. In addition we will take following steps to minimize the risk.

### **Minimization of Risk**

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

1. Physicians and staff will receive appropriate training prior to using the system. Training will include instruction on equipment and lab setup, assessing renal anatomy, intra-procedural patient management and monitoring, Symplicity Catheter delivery and RF ablation, and post-procedural care.
2. The system's design and software include several safety mechanisms to reduce risk to the patient (limitations on temperature, time, impedance, and power delivered to the patient).

3. Patients will be closely monitored during the procedure and at regularly scheduled intervals for the duration of the study.
4. Physicians will employ usual and customary clinical technique (e.g., sterile technique during catheter use and aseptic wound care procedures).
5. Appropriate sedatives and narcotics will be used during the procedure to minimize discomfort associated with the shock.
6. During follow-up sessions, any side effects will be identified and treated accordingly.

**Table 3. Safety events at 6 and 12 months.**

Safety measures, n (%)		6 months (n=50)	12 months (n=49)
Death*		0 (0%)	0 (0%)
Cardiovascular events	Myocardial infarction	1 (2%)	1 (2%)
	Hypertensive crisis/emergency*	0 (0%)	0 (0%)
	Stroke	0 (0%)	0 (0%)
	Hospitalisation for new onset heart failure	0 (0%)	0 (0%)
	Hospitalisation for atrial fibrillation	0 (0%)	0 (0%)
Renal events	Renal artery reintervention due to perforation or dissection*	0 (0%)	0 (0%)
	New onset end-stage renal disease*	0 (0%)	0 (0%)
	Serum creatinine elevation >50%	(2) 4%	(2) 4.1%
	Significant embolic event resulting in end-organ damage*	0 (0%)	0 (0%)
	New renal artery stenosis >70%*	0 (0%)	0 (0%)
Post-procedural events	Vascular complications*	3 (6.0%)¶	

Numbers are defined as mean±standard deviation or no. (%). \*The major adverse event rate is 6% (3/50 events) and defined as the one-month rate of all safety events and the six-month rate of new renal artery stenosis >70% as shown with asterisks. ¶Three patients with pseudoaneurysm, two of whom also had haematoma.

**Table 1: Safety evaluation of Symplicity™ multi-electrode radiofrequency renal denervation system (20)**

## Measures

Following measures will be taken at baseline, 6 weeks and 3 and 6 month after the procedure:

**EQ-5D™:** A descriptive questionnaire with 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The dimensions have five levels (no, slight, moderate, severe and extreme problems). Participants select the level that corresponds to their perceived health status. Also, there is a vertical visual analogue scale (VAS) from 0 to 100, where participants record their health status lies with the end points being "The worst health you can imagine" and "The best health you can imagine". The VAS results may be used to quantify the patient's judgement on their own health.

**McGill Pain Questionnaire (MPQ):** A questionnaire to measure the quality and quantity of patient pain. The scale ranges from no pain (0) to maximum pain (78).

**Brief Pain Inventory Questionnaire (BPS):** A questionnaire to measure the severity and impact of pain on the patient's daily life and the perceived relief received from current intervention. The short form is has nine-points relating to patients occurrence of pain, areas of pain, rating pain at its worst in the last 24 hours, rating pain at its least in the last 24 hours, average pain level, current pain level, treatments being used, percentage of pain relief form medications used in the past 24 hours and specification of how pain has interfered with life.

**CES-D:** A questionnaire for measuring self-reported depression. Patients are asked to rate over the last week how often they experienced symptoms of depression. Scores range from 0 to 60, with higher score indicating more depression symptoms and lower scores indicating fewer symptoms.

**Short Form Health Survey (SF-36):** A health-related quality of life questionnaire that elicits information about participants using eight health concepts: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. Scores range from 0 to 100, with lower scores relating to more disability and higher scores relating to less disability.

**Oswestry Disability Index (ODI):** A health questionnaire used to measure patient's functional disability. The questionnaire comprises of ten sections: pain intensity, personal care, lifting, walking, sitting, standing sleeping, sex life, social life and travelling. Index scores range from 0% to 100%, with higher scores relating to more disability and lower scores relating to less disability.

**Pain Medication Diary:** Participants will be asked to record the number and doses of medications they are taking to alleviate their pain. The type of medication will also be recorded.



**SCID-5:** A structured assessment tool for DSM-5 disorders (exclusion criteria for the present study). The diagnostic modules can assess somatic symptom disorders, mood disorders, psychotic disorders, substance use disorders, obsessive compulsive and related disorders, anxiety disorders, eating disorders, some sleeping disorders, externalizing disorders and trauma and stress related disorders. For six weeks and three and six-month assessment we will follow up with the patient, by phone or by in-person visit.

### **Participant's Follow-up Regimen**

Participants will have the initial treatment of either RDN or the sham procedure and be followed for 6 months. After this time has elapsed and the treatment allocation is unblinded, participants who received the sham procedure will be given the RDN procedure. Participants will initially have their baseline measurements taken (pain score (MPQ, BPS)), quality of life scores (EQ-5D, SF-36), mood (CES-D), and disability (ODI) and then have follow-ups taken at 6 weeks, 3 and 6 months post treatment. Participant's demographic data (age, gender and race), complete blood count, serum electrolytes, and serum urea/creatinine and urine analysis, BMI and eGFR will also be collected.

### **Participant's Safety/Discontinuation**

An independent safety committee will be formed to formatively assess risks to patient safety throughout the study. The committee will consist of physicians, researchers and administrators whom are not involved in the study, and have extensive nephrology and/or research experience. The committee will meet before recruitment, upon randomization, bi-weekly during the procedure period, and post-procedure. For participant's safety we will be sending data to independent researcher at 6 week, 3 and 6 month after the procedure. Exactly same procedure will be followed for participants in sham group, after unbinding of the study, for renal denervation treatment.

Participants are allowed to withdraw from the study at any time without need to explain. Should the independent safety committee report patient safety concerns, the decision will be made as to whether the trial should be discontinued or whether the consent form must be modified to incorporate any new findings. Should new findings about the efficacy of this procedure for this indication emerge that would impact the premise for the study, the appropriateness of continuing the study will be reviewed. Should an emergency situation occur, the manager of the radiology suite who has access to the randomisation schedule will give the principal investigator the name, ID and treatment allocation of the participant involved in the emergency condition. The principal investigator will decide if there is an emergency with his experience as a physician. The research team has applied for

biomedical research ethics approval from the Regina Qu'Appelle Health Region (RQHR) Research Ethics Board.

## **Statistics**

Analysis for the feasibility trial will be restricted to qualitative thematic analysis and non-parametric analysis to compare the two small patient populations. No power or sample size calculations will be reported as this is not necessary for the feasibility phase of this trial.

## **Study Timeline**

---

Study will commence only after getting approval from Health Canada. This study has been reviewed by Research Ethics Board, Regina and given provisional approval subject to the submission of No Objection letter from Health Canada.

The estimated duration of the study is 18 months. We plan to recruit patients in summer/fall 2018, with the treatment and control procedures conducted in the winter of 2018. This study involves a follow-up of six months from baseline. After this point, participants in the control group will go for the renal denervation treatment and will be followed for six month post procedure. Analysis and knowledge translation activities will occur after all follow-up are done. Please see the attached study scheme and timeline in Appendices folder.

All procedures will be carried out by an interventional radiologist at the Regina General Hospital. Confirmation of LPHS diagnosis and eligibility screening will be done by the Principal Investigator a nephrologist at Regina General Hospital. Recruitment will then be conducted by a Nurse Practitioner based on the eligibility criteria, in conjunction with the Principal Investigator. Baseline and follow-up data collection will be done by Nurse Practitioner involved in the study. This clinical team is already well trained in this procedure and have already published a case-study report on the topic in addition to the pre/post cohort study, which was presented at an international medical conference and published<sup>15,16</sup> Research Scientist involve in the study will conduct the feasibility measure assessments, data entry, analysis and knowledge translation support. In-kind research support from Research and performance support will provide coordination and analysis services throughout the duration of the study.

## **Strengths/Weaknesses**

---

## **Strengths**

Our study is a blinded, randomized controlled, crossover feasibility trial which will remove much potential bias that may affect the perceived effectiveness of RDN on LPHS patients. We will be measuring patient outcomes at three different time points, up to six months post intervention, so we may find how patient self-reported pain and quality of life may change over time following the procedure.

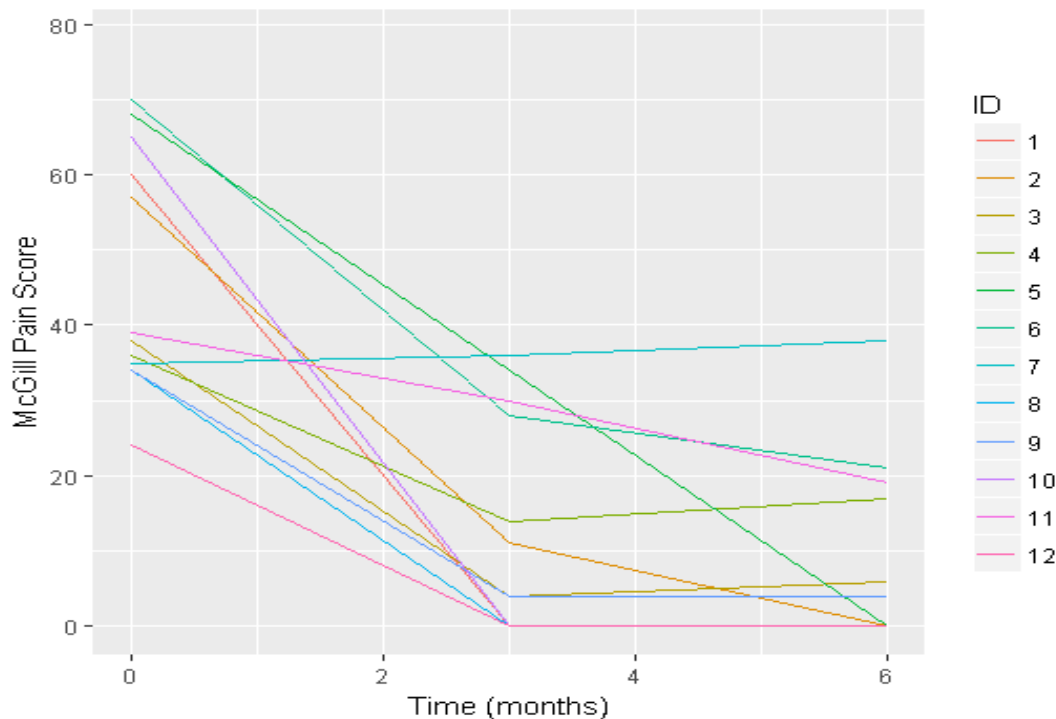
## **Weaknesses**

Patients will be followed for up to 6 months following treatments, so we will not be able to discern treatment effectiveness long-term in LPHS patients.

## **Progress and clinical experience**

---

Our team has produced two manuscripts <sup>15,16</sup> regarding the impact of renal denervation on LPHS patients. The first article published in the American Journal of Kidney Disease, reported four successful cases, where "50% patients experienced complete pain relief post procedure, whereas the rest of the 50% patients had a 75% improvement in their frequency of analgesic use." <sup>15</sup> We have since published a 12-patient cohort study in Kidney International Reports, where we reported that 10/12 patients at 3 months and 11/12 patients at 6 months had >30% reduction in pain based on the McGill pain questionnaire, along with consistent improvements in disability, mood and quality of life. <sup>16</sup> Our pain reduction results from the 12-person single arm study are summarized in Figure 1. These results provided us with sufficient preliminary data to scale our hypothesis, improve our study design, and introduce more rigors to our methods so we may use an RCT design to more-definitively assess the effectiveness of renal denervation on pain reduction for LPHS patients.



**Figure1. McGill pain scores (0-78 max pain) at baseline and at 3 and 6 months post renal denervation treatment in 12 LPHS patient.**

## References

1. Eisenberg ML, Lee KL, Zumurutbas AE, Meng MV, Freise CE, Stoller ML. Long-term outcomes and late complications of laparoscopic nephrectomy with renal autotransplantation. *J Urol.* 2008;179(1):240-243.
2. Little PJ, Sloper JS, de Wardener HE. A syndrome of loin pain and haematuria associated with disease of peripheral renal arteries. *Q J Med.* 1967;36(142):253-259.
3. Lall R, Mailis A, Rapoport A. Hematuria-loin pain syndrome: Its existence as a discrete clinicopathological entity cannot be supported. *Clin J Pain.* 1997;13(2):171-177.
4. Ammons WS. Renal afferent input to thoracolumbar spinal neurons of the cat. *Am J Physiol.* 1986;250(3 Pt 2): R435- 43.
5. Ammons WS. Bowditch lecture. renal afferent inputs to ascending spinal pathways. *Am J Physiol.* 1992;262(2 Pt 2): R165-76.

6. Kadi N, Mains E, Townell N, Nabi G. Transperitoneal laparoscopic renal denervation for the management of loin pain haematuria syndrome. *Minim Invasive Ther Allied Technol.* 2013;22(6):346-351.
7. Grech AK. Loin Pain Haematuria Syndrome - A Narrative Review of Pain Management Strategies. *Korean J Pain.* 2016 Apr; 29(2):78-85.
8. Zubair AS, Salameh H, Erickson SB, Prieto M. Loin pain hematuria syndrome. *Clin Kidney J.* 2016 Feb;9(1):128-34.
9. Bultitude, M.I. Capsaicin in treatment of loin pain/haematuria syndrome. *Lancet.* 1995;345:921–922.
10. Dimski DS, Hebert LA, Sedmak D, et al. Renal autotransplantation in the loin pain-hematuria syndrome: A cautionary note. *Am J Kidney Dis.* 1992;20(2):180-184.
11. Bultitude MI. Capsaicin in treatment of loin pain/haematuria syndrome. *Lancet.* 1995;345(8954):921-922.
12. Uzoh CC, Kumar V, Timoney AG. The use of capsaicin in loin pain-haematuria syndrome. *BJU Int.* 2009;103(2):236- 239.
13. Blacklock AR. Renal denervation with releasing renal capsule incision in the loin pain/haematuria syndrome. *Br J Urol.* 1989;64(2):203-204.
14. Andrews BT, Jones NF, Browse NL. The use of surgical sympathectomy in the treatment of chronic renal pain. *Br J Urol.* 1997;80(1):6-10.
15. Prasad B, Giebel S, Garcia F, Goyal K, St Onge JR. Renal denervation in Patients with Loin Pain Hematuria Syndrome. *Am J Kidney Dis.* 2017 Jan; 69(1):156-159.
16. Prasad B, Giebel S, Garcia F, Goyal K, Shrivastava P, Berry W. Successful Use of Renal Denervation in Patients with Loin Pain Hematuria Syndrome—The Regina Loin Pain Hematuria Syndrome Study. Volume 3, Issue 3, May 2018, Pages 638-644.
17. Ashe MC, Winters M, Hoppmann CA, Dawes MG, Gardiner PA, Giangregorio LM, Madden KM, McAllister MM, Wong G, Puyat JH, Singer J, Sims-Gould J, McKay HA. "Not just another talking program": Everyday Activity Supports You (EASY) Model – a randomized pilot study for a parallel randomized controlled trial. *BMC Pilot and Feasibility Studies.* 2015; 1:4.
18. Donovan JL, Rooshenas L, Jepson M, Elliot D, Wade J, Avery K, Mills N, Wilson C, Paramasivan S & Blazeby JM. Optimizing recruitment and informed consent in randomized controlled trials: The development and implementation of the Quintet Recruitment Intervention (QRI). *BMC Trials.* 2016; 17:283.

19. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, Lancaster GA. CONSORT 2010 statement: Extension to randomized pilot and feasibility trials. *British Medical Journal*. 2016; 355.
20. Robert Whitbourn<sup>1\*</sup>, MBBS, BMedSc, BSc; Scott A. Harding<sup>2</sup>, MB ChB, MD; Antony Walton<sup>3</sup>, MD. Symplicity multi-electrode radiofrequency renal denervation system feasibility study. *Euro Intervention* 2015; 11:104-109.