Prostatic Artery Embolization vs Medication for Benign Prostatic Hyperplasia: Single Subject Study Design

NCT number NCT04398966
Document Date 03/11/2022

PROTOCOL TITLE
Prostatic Artery Embolization vs Medication for Benign Prostatic Hyperplasia: Single Subject Study Design

Principal Investigator
Clayton Commander, MD (UNC-Chapel Hill, Radiology)
(850) 758-1998 (PHONE)
Email: clayton_commander@med.unc.edu

Co-Investigators
Hyeon Yu, MD
Matthew Raynor, MD

Biostatistician
Thad Benefield, MS (UNC-Chapel Hill, Radiology)

Sponsor: University of North Carolina

Funding Source: Terumo Interventional Systems

Version Date: March 11, 2022

PROTOCOL TITLE
Prostatic Artery Embolization vs Medication for Benign Prostatic Hyperplasia: Single Subject Study Design

Principal Investigator
Clayton Commander, MD (UNC-Chapel Hill, Radiology)
(850) 758-1998 (PHONE)
Email: clayton_commander@med.unc.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

Date of Protocol: March 11, 2022

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
PAE	prostatic artery embolization
BPH	Benign prostatic hyperplasia
CT	computed tomography
MRI	magnetic resonance imaging
IPSS	international prostate symptom score
LUTS	lower urinary tract symptoms
Qmax	peak urine flow rate
PVR	post void residual

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This will be a single arm, uncontrolled, non-blinded study of PAE using HydroPearl Beads in a small population of 30 subjects with benign prostate hyperplasia (BPH) to investigate the effectiveness of prostatic artery embolization (PAE) relative to previous medication alone for reducing urinary symptoms due to BPH. Secondary aims will be to assess adverse effects of medication vs adverse events secondary to PAE as well as Quality of Life scores on medication vs after PAE.

1.2 Disease Background

Over the past 7 years, data has emerged from numerous countries supporting the safety and efficacy of prostatic artery embolization (PAE) for the treatment of lower urinary tract symptoms (LUTS) in the setting of benign prostatic hyperplasia (BPH) (1). In response, the Food and Drug Administration (FDA) recently granted a de novo classification to Merit Medical Systems to expand the indications for Embosphere Microspheres to include PAE for the treatment of BPH. Moreover, it has given 510(k) clearances to both Embozene Microspheres and HydroPearl Microspheres.

Medication is the first line therapy for lower urinary tract symptoms (LUTS) secondary to BPH. These medications include alpha-adrenergic inhibitors, 5-alpha reductase inhibitors and phosphodiesterase inhibitors. While these medications are effective in improving urination in many men, there are also troubling side effects including retrograde ejaculation, erectile dysfunction, gynecomastia, lightheadedness, nasal congestion and loss of libido. Because of these side effects many men will discontinue the use of these medications.

It has been shown that PAE is very unlikely to result in a major complication and the minor complications tend to resolve without treatment within several weeks of the procedure. Therefore, because of its safety, and the untoward effects of BPH medications, it may be reasonable to suggest that PAE could be substituted as first line treatment for BPH. To further explore this notion, research comparing PAE to medication is needed.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary aim of this study is to determine if PAE will result in a reduction of urinary symptoms similar to medication in individual patients.

2.2 Secondary Objectives

The secondary aims are to determine if PAE will result in less adverse events compared to medication in individual patients and to determine if self assessed quality of life is better on medication or after PAE.

2.3 Outcome Variable

2.3.1 Primary Study Outcome Variable

Reduction in IPSS at 6-month follow-up.

2.3.2 Secondary Study Outcome Variable

1. Improvement of QoL score at 6 months
2. Improvement of uroflowmetry (Qmax, PVR) at 6 months
3. Reduction of prostate volume at 6 months
4. Percentage of prostate infarcted at 6 months
5. Incidence of adverse events at 3 months

3.0 PATIENT ELIGIBILITY

Study subjects will be men with benign prostatic hyperplasia who have been taking an alpha-blocker, a 5-alpha reductase inhibitor or both for at least 6 months.

Thirty (30) subjects will be enrolled and all are anticipated to complete the study.

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

3.1.1 Male

3.1.2 Age ≥ 40

3.1.3 Prostate gland measures ≥50 grams measured by MRI, CT, or ultrasound

3.1.4 Currently taking BPH medications including either alpha blockers, 5-alpha reductase inhibitors or the combination of both for no less than 6 months

3.1.5 Capable of giving informed consent

3.1.6 Life expectancy greater than 1 year

3.2 Exclusion Criteria

All subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

3.2.1 Severe vascular disease as defined by severe arterial calcification seen on prior imaging, history of lower extremity or pelvic bypass grafts or history of lower extremity or pelvic arterial stenting. For patients that do not have prior imaging at

UNC, we will rule out suspected severe arterial calcification given their medical history.

3.2.2 Uncontrolled diabetes mellitus which is defined as A1C >8%

3.2.3 Patients currently taking SGLT2 inhibitors (cana-, dapa-, empa-, and ertu-gliflozin) due to their diuretic effects

3.2.4 A smoking history of 20 pack-year or greater obtained by patient report

3.2.5 Prior myocardial infarction

3.2.6 A stroke within the last 6 months

3.2.7 Unstable angina

3.2.8 Immunosuppression

3.2.9 Neurogenic bladder and/or sphincter abnormalities secondary to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes, etc.

3.2.10 Complete urinary retention

3.2.11 Impaired kidney function (serum creatinine level > 1.8 mg/dl or a glomerular filtration rate < 60 as approximated using serum creatinine levels) unless anuric and on dialysis.

3.2.12 Confirmed or suspected bladder cancer as assessed based on patients' medical history or current hematuria

3.2.13 Urethral strictures, bladder neck contracture, or other potentially confounding bladder pathology

3.2.14 Ongoing urogenital infection. For patients with symptoms of a urogenital infection (dysuria, fever, etc.), a urinalysis will be obtained.

3.2.15 Previous pelvic radiation or radical pelvic surgery

3.2.16 Confirmed malignancy of the prostate or a history of prostate cancer

3.2.17 Contrast hypersensitivity refractory to standard medications (antihistamines, steroids)

4.0 STUDY PLAN

4.1 Study Procedures

4.1.1 Study Design

This will be a single arm, non-blinded study of PAE in a small population with BPH to determine if PAE is as effective as medication (non-inferiority) in reducing urinary symptoms due to BPH. After IRB approval of a written informed consent and over approximately a 24 month duration, a total of N=30 subjects will be recruited at 3 sites. Only subjects ≥ 40 years will be screened for study recruitment. Clinical procedures and evaluations will consist of a preoperative screening assessment to determine if the potential study subject meets the inclusion and exclusion criteria, enrollment, surgical procedure for prostatic artery embolization (PAE), and follow-up visits at 24 hours, 1 week, 3, 6, & 12 months. An MRI will be performed after the 6-month visit in those patients who underwent embolization to detect a change in prostatic volume and perfusion and to exclude complication.

4.1.2 Study Treatment

Subjects will be given a dose of antibiotics on the day of the procedure (Bactrim 400mg/80mg or Cipro 500 mg if the patient has an allergy to sulfa drugs. Additionally, non-steroidal anti-inflammatory medication will be administered on the day of procedure (500 mg Naproxen). The patients will be given the choice of receiving intravenous anxiolytic and analgesic medication during procedure or proceeding with local anesthetic only.

Ultrasound-guided access into common femoral artery or radial artery will be obtained. An intra-arterial sheath will be placed. Through this sheath a diagnostic catheter will be used to perform pelvic angiography. Additionally, a cone beam CT angiogram may be performed. Based on these images and CT angiography obtained before the procedure, a microcatheter will be fluoroscopically guided into the prostatic artery. HydroPearl® microspheres (ranging from 75-400um based on the operator's discretion) will then be injected under fluoroscopic guidance to prevent reflux and non-target embolization. Injection will continue until there is stasis. The catheter will then be guided into the contralateral prostatic artery and repeat embolization will be performed until stasis. If necessary, extraprostatic arterial anastomoses will be embolized with a coil to protect against non-target embolization. The catheter and sheath will then be removed and hemostasis will be achieved with compression or an intra-arterial closure device. The subject subsequently will be discharged home the same day or the following day.

It is anticipated that less than 4 milliliters of HydroPearl® microspheres will be required for bilateral embolization. The size of the bead (75- 400 μm) will be dependent on the operator's determination of what is most appropriate based on the size of the prostate and the prostatic vessels. The range in size of particles will allow the operators to discern the safest, most effective size for the vessels targeted. Embolic size will be based on the overall size of the prostate, size of the

target vessels, and likelihood of non-target embolization. For example, depending on how far the catheter can be advanced, smaller particles can be safely used to induce ischemia in the target tissue. This concept is utilized routinely within embolization procedures are commonly performed.

4.1.3 Method for Assigning Subject to Treatment Groups

All subjects will receive the intervention.

4.1.4 Prior and Concomitant Therapy

The subjects will be required to have been on medical therapy for BPH for at least six months prior to undergoing PAE. Such medications include alpha blockers, 5-ARIs or combination therapy. The medication usage will be stopped by the 3 month visit in order to allow an adequate washout period for 5-ARI's prior to the 6 –month visit.

4.1.5 Enrollment/Recruitment

Subjects will be recruited from the urology and vascular & interventional radiology (IR) clinics across three (3) sites.

4.1.6 Screening Visit (Visit 1)

If a patient qualifies to be a subject in the study based on the inclusion and exclusion criteria listed in section 3.1 and 3.2, the study coordinator will be notified. The coordinator will review the study with the patient and obtain written informed consent. Once the subject is enrolled in the study, he will be seen by one of the co-investigators in either the IR or Urology clinics at one of the study sites. The procedure will be again described to the patient and any questions will be answered. International Prostate Symptoms Survey (IPSS) with Quality of Life (QOL) questionnaires and Qmax and PVR measurements will be obtained if not completed in the prior 3 months during the pre-study work-up. Study specific questionnaires to assess medication usage will also be completed. A MRI of the pelvis with and without contrast will be ordered and obtained prior to visit 2 for baseline evaluation of the prostate unless the patient has one from the prior 6 months. If the patient had a contrast enhanced MRI of the pelvis within the past 6 months, this MRI will be used.

4.1.7 Visit 2 - PAE Procedure

PAE procedure will be performed as described in part 4.1.2 above within 8 weeks of Visit 1. Subjects will be given a pager number to reach a physician (24 hours a day) to report any adverse symptoms and receive medical advice.

Patients will be asked medication history questionnaire at this visit prior to the procedure.

4.1.8 Visit 3 -1 Day Follow-up

Subjects will be seen in clinic or contacted by phone or by teleconference, per the subject's preference, the day following PAE procedure (+3 days). As most

complications of the procedure will be evident within this time, this visit is to evaluate for early AEs. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI or CT.

4.1.9 Visit 4 -1 Week Follow-up

Subjects will be seen in clinic or contacted by phone or by teleconference, per the subject's preference, one week following PAE procedure (+5 days). As most complications of the procedure will be evident within this time, this visit is to evaluate for early AEs. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI or CT.

4.1.10 Visit 5 - 3 Month Follow-Up

Subjects will return 90 +/- 14 days after PAE procedure to complete IPSS, and QOL questionnaires; to have Qmax and PVR measured; medication history questionnaires will be completed; and subjects will be evaluated for possible adverse events. It will be recorded if subjects are unable to hold medications at this time due to residual urinary symptoms. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed.

4.1.11 Visit 6 - 6 Month Follow-Up

Subjects will return 180 +/- 14 days after PAE procedure to complete IPSS with QOL and medication history questionnaires and to have Qmax and PVR measured. The subjects will be evaluated for possible adverse events. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed.

An MRI of the prostate will be acquired.

4.1.12 Visit 7– 12 month follow-up for all subjects

Subjects will return 360 days +/- 14 days after PAE to complete IPSS and QOL questionnaires and to have Qmax and PVR measured.

4.1.13 Subject Compliance Monitoring

Study coordinators and physicians will inquire of the subjects to determine if they have escalated any current or initiated any new conservative therapies during the follow-up period.

4.1.14 Criteria for Removal from Study

Subjects will be withdrawn from the study if a major complication occurs that prevents completion of PAE or the ability to complete the follow up visits.

Patients may also withdraw at any point at their discretion. Data will be included with an intent to treat analysis. Reasons for study withdrawal will be recorded.

4.1.15 Follow-up for Withdrawn Subjects

If a subject withdraws from the study, any recorded data will still be included in the analysis. Subjects will only be replaced if they withdrew prior to undergoing PAE.

4.2 Safety and Effectiveness Assessments

4.2.1 Safety Assessments

Subjects will be observed for several hours after PAE to monitor for immediate complications to include bleeding, infection and acute ischemia of the rectum and bladder. Subjects will be contacted by study personnel the day after PAE to inquire about delayed onset complications. The subjects will also be given a phone number that they can call to reach a nurse if they believe they have developed a complication of the procedure.

4.2.2 Effectiveness Assessments

Technical success will be defined as bilateral prostatic artery embolization. This will be determined during the procedure. Clinical success will be defined as an IPSS score reported at the 6-month visit that is equal to or less than the pre-PAE baseline score. The size of the prostate will be measured by MRI at 6-month follow-up visit. IPSS, QoL, PVR and Qmax will be measured at 3, 6 and 12-month follow-ups.

4.3 Time and Events Table

	Visit 1 (Screening)	Visit 2 (Procedure)	Visit 3 (1 Day)	Visit 4 (1 week)	Visit 5 (3 month)	Visit 6 (6 Month)	Visit 7 (12 month)
Informed Consent	X						
MRI	X					X	
PAE procedure		X					
IPSS w/QOL	X				X	X	X
Qmax	X				X	X	X
PVR	X				X	X	X
Medication History Questionnaire	X	X			X	X	
AE Assessment			X	X	X	X	

5.0 DEVICE

5.1 Name of Device

HydroPearl® compressible microspheres (75 to 400 μm)

5.2 Intended Use of the Device

HydroPearl® compressible microspheres (75 to 400 μm) will be used for prostatic artery embolization in patients with BPH consistent with labeling.

5.3 Description of the Device

HydroPearl® compressible microspheres are part of a family of embolic materials based on Microvention's proprietary microsphere technology. These spheres are designed to offer controlled, targeted embolization. HydroPearl microspheres are made using Poly-Ethylene Glycol and are precisely calibrated, non-resorbable, hydrophilic, compressible, and biocompatible. HydroPearl® microspheres are available from 75-1100 μm and are provided in a sterile syringe pre-filled with microspheres in phosphate buffered saline.

The HydroPearl® compressible microspheres are intended for the embolization of arteriovenous malformations and hypervascular tumors, including uterine fibroids and benign prostatic hyperplasia.

- HydroPearl® compressible microspheres are contained in a sterile 20 cc pre-filled syringe and packaged in a pre-formed tray with Tyvek peel-away lid.
- Each syringe contains approximately 2 ml of HydroPearl compressible microspheres in non-pyrogenic, sterile, transport solution of physiological buffered saline.
- The product is packaged sterile. Do not use if the unit package is opened or damaged.
- Each syringe is intended for a single patient use only. Do not re-sterilize. Discard any unused material.

Once a catheter has been fluoroscopically guided into the target vessel, the embolization spheres are then injected, causing obstruction at the arteriole level until the desired degree of embolization has occurred. The embolization spheres used during the study will be unchanged.

5.4 Expected Risks

A recent meta-analysis of PAE data from 662 patients in nine studies reported only two major complication (0.3% major complication rate) involving bladder ischemia requiring surgery and severe urinary sepsis requiring hospitalization. Among minor complications transient rectalgia and/or dysuria (9.1%), acute urinary rentention (7.9%) and transient hematuria (4.4%) were the most common (1).

Detailed risk analysis is below:

	Risk or Side Effect	Source of Risk or Side Effect	Possible	Less Possible	Rare Events
Potential Risks Associated Study Enrollment & Study Procedures	Discomfort	Blood draw for lab test, ultrasound or MRI	X		
	Thrombophlebitis, bruising, bleeding, blood clot, Pre-syncope or Syncope (i.e. Fainting)	Blood draw for lab tests		X	
	Anxiety or Claustrophobia	MRI scan		X	
	Psychological Discomfort	Clinical Trial			X
	Infection	Blood draw for lab tests			X
	Allergic Reaction	MRI contrast			X
	Gadolinium contrast adverse reaction (i.e. Nephrogenic Systemic Fibrosis or severe skin reaction from contrast agent only reported in patients with kidney dysfunction)	MRI Contrast injection			X
	Confidentiality breach from Medical Records	Medical Record Keeping			X
	Groin/Anesthetic Injection/Neurologic Injury/	Pressure during arterial access and	X		
	Discomfort/Pain	after catheter removed at the leg/femoral artery site	X		
Risks of the PAE	Radiation Exposure Injury	PAE procedure			X
	Kidney Dysfunction	Contrast injected during procedure		X	
	Infection	PAE Procedure		X	

Procedure and Post-operative care	Adverse or Allergic Reaction	Intravenous contrast agent or medications administered as part of procedure or follow-up care (ie. MRI contrast)		X	
	Tissue damage to Skin, Muscle, Skin or other structure in legs and groin (Non-target Embolization)	PAE procedure			X
	Minor Bruising or Bleeding	PAE procedure			X
	Bleeding requiring Transfusion or surgery	PAE procedure			X
	Post Embolization Syndrome, including fever, malaise, headache, and myalgia (body aches)	PAE procedure		X	
	Internal bleeding, such as Gastrointestinal bleeding	Medications taken after the procedure (i.e. Ibuprofen)			X
	Infection	Catheter site in the leg/groin			X
	Arterial injury/trauma, laceration, bruising/pseudo aneurysm	Procedure/ Closure device (clip) on the artery			X
	Pulmonary embolism (clot in lung), Thrombophlebitis (clot in artery or vein)	PAE procedure			X
	Myocardial Infarction (Heart attack)	PAE procedure including moderate sedation/sedative medication			X
	Stroke	PAE procedure including moderate sedation/sedative medication			X

	Disability	PAE procedure including moderate sedation/sedative			X
	Death	PAE procedure including moderate sedation/sedative medication			X

5.5 Risk Minimization

The PAE procedure will be performed by board-certified interventional radiologists who have expertise in endovascular techniques, particularly in selective catheterization and transcatheter embolization techniques. Analgesia during the procedures will be provided through the use of conscious sedation if required. The risks of conscious sedation will be minimized by continuous monitoring of heart rate, blood pressure, oxygen saturation, and cardiac rhythm. The dose area product projected for the procedure is thought to be less than 30 gray/cm2 which is about 2-4 years of background radiation and significantly less than that of a cardiac catheterization. Radiation exposure will be minimized to subjects under the principal of 'as low as reasonably achievable' (ALARA).

Sterile instruments with a sterile technique will be used to minimize infection risk at the arterial access site. Pre-operative antibiotic(s) will be administered to reduce risk of other infections, such as urinary tract. The arterial access site discomfort will be minimized by administration of local anesthesia into the overlying skin and adjacent tissues. Catheter access into the appropriate artery may be performed using ultrasound-guided arterial puncture to prevent inadvertent vessel puncture with subsequent bleeding. Real-time fluoroscopic monitoring of all catheter/wire manipulations will be used to prevent vascular injury.

The subject will be monitored for the risk of an allergic response to iodinated contrast. To minimize the risk of renal dysfunction there will be use of non-ionic contrast agents, and appropriate pre-procedure hydration, when necessary. Subjects who report an allergic reaction to iodinated contrast will be pre-medicated as per routine allergy prophylaxis per standard of care.

5.6 Receiving, Storage, Dispensing and Return

5.6.1 Receipt of Supplies

Terumo will provide, at no charge, up to 10 boxes (5 vials/box) of HydroPearl® microspheres for the Study ("Devices"). HydroPearl® microspheres will be stored within the Interventional Radiology Department in a separate area. Embolic devices will be labeled 'for investigational use only' and will be reserved for use in the clinical trial.

5.6.2 Storage

HydroPearl® microspheres must be stored in a cool, dark, dry place in their original packing.

5.6.3 Dispensing

No study specific dispensing techniques will be used.

5.6.4 Return or Destruction of Device

The Institution and Sponsor-Investigator shall, return any such Product to Company promptly if requested by the Company upon the completion or termination of the Study for which such Product was being utilized, or promptly dispose of or destroy, as the Company may reasonably direct, all of its remaining stocks of Product. All Devices supplied by Terumo to Institution for the Study shall be used by Institution only as specified in the Protocol and the Clinical Trial Agreement. No other use of the Devices is authorized.

Disposable syringes, which spherical particulate is stored in, will be discarded as medical waste and packaging will be kept in a secure location until the study is completed. Packages will be disposed of upon completion of the study.

Lot numbers of the device used will be recorded in the CRFs for the study procedure.

6.0 UNANTICIPATED CONCERNS (DEVICES)

6.1 Unanticipated Adverse Device Effect (UADE)

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

6.2 Unanticipated Problems (UP)

As defined by UNC's IRB, unanticipated problems involving risks to study subjects refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

6.3 Reporting

6.3.1 UADEs

UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

For this device study, investigators are required to submit a report of a UADE to the FDA, the manufacturer of the device and the UNC IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)), using the MedWatch Form 3500A. Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, the UNC IRB, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

For this device study, we will submit a report of a UADE to the manufacturer and the IRB as soon as possible, but no later than 10 working days after the investigators first learn of the event.

6.3.2 UP

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the clinical investigator using the IRB's web-based reporting system.

Any unanticipated problem that occurs during the conduct of this study and that meets **at least** the first two criteria listed in section 6.2 must be reported to the UNC IRB using the IRB's web-based reporting system.

7.0 ADVERSE EVENTS (DRUGS- CONTRAST AGENTS)

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);

- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout.

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

7.3.2 Documentation and Notification

These events (SAEs or Serious SARs) must be recorded within 24 hours of learning of its occurrence.

7.3.3 Reporting

IRB Reporting Requirements:

The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

The primary study aim is to determine if PAE is as effective as medication (non-inferiority) in reducing urinary symptoms due to BPH at 6 months.

This will be a single arm, non-blinded study of PAE using HydroPearl Beads in a small population with BPH to assess a clinically significant reduction in medications at 6 months. After IRB approval of a written informed consent and over, approximately a 24 month duration, N=30 subjects will be recruited. Only subjects ≥ 40 years will be screened for study recruitment. Clinical procedures and evaluations will consist of a preoperative screening assessment to determine if the potential study subject meets the inclusion and exclusion criteria, enrollment, surgical procedure for prostatic artery embolization (PAE), and follow-up visits at 24 hours, 1 week, 3, 6, & 12 months. An MRI will be performed after the 6-month visit in those patients who underwent embolization to detect a change in prostatic volume and perfusion and to exclude complication.

The study will be stopped if there is greater than one major complication (Grade D, E or F) as defined by the Society of Interventional Radiology Classification System for Complications by Outcome (29).

8.2 Sample Size Rationale

Prior studies have demonstrated larger decreases in IPSS scores using PAE, compared to medication alone. Abt found the mean decrease in IPSS to be 9.23 for PAE with standard deviations of IPSS scores being 5.7 at baseline and after treatment (18). Lepor found a decrease in IPSS attributable to medications of 6.6 (17).

We set a 10% non-inferiority margin and expect the correlation of IPSS scores between screening and 6-months to be high. Assuming a correlation of .65.we will have 81.2% power to test the non-inferiority hypothesis with an alpha of 0.025 for our 30 budgeted pairs, assuming 20% dropout (pairs=subjects given single subject study design).

Power calculations used PROC POWER, SAS, Version 9.4. This sample size is adequately large to address the study's primary aim with reasonably large power.

8.3 Data Analysis Plans

A patient will be considered an evaluable study subject evaluable for data analysis per the following criteria, a written informed consent was obtained, he meets the inclusion and exclusion criteria, and received the PAE study procedure. All subjects with 12-month follow-up data will be included for analysis even if some follow up data is incomplete. Every attempt will be made to ensure that there is as

little missing data as possible including reminder phone calls and follow-up phone calls, if a subject misses a visit.

The primary aim is to demonstrate non-inferiority of PAE compared to medication with respect to the outcome measure IPSS. We assumed a non-inferiority margin of 10%, in line with the FDA's recommendations, since similar prior non-inferiority trials were unavailable. The null hypothesis states that in the target population mean IPSS is at least 10% greater at 6 months post-treatment than at baseline (pre-treatment). The alternative hypothesis will be that the mean IPSS at 6 months is less than or equal to 10% greater than the mean IPSS at screening.

To address this hypothesis we will implement a random effects linear model, modeling IPSS score as a function of time and the indicator of whether medication had stopped by the time of the 3-month follow-up. We will include an R-side compound symmetric random effect to account for patient-level correlation. We will compute the predicted mean and standard deviation(SD) of IPSS at screening and 6 months; the difference of the predicted mean IPSS score, defined as the mean IPSS at 6 months minus the mean IPSS at screening; and the SD of this difference. Point estimates of these values will be reported along with 95% confidence intervals for the mean difference.

A non-inferiority p-value <0.05 testing whether the difference in the predicted mean at screening is at least 10% greater than the predicted mean of IPSS at screeningwill be considered evidence against the null hypothesis of inferiority of PAE, compared to treatment. A non-inferiority p-value >0.05 will be considered inconclusive evidence against inferiority.

As a sensitivity analysis for the primary aim, we will repeat the same model outlined above after removing patients from the analysis who were still taking medications at the 3-month follow-up. Point estimates, confidence intervals, and p-values will be compared against those obtained in the primary analysis.

To address the secondary aim, we will tabulate the proportion of patients AEs pre- and post-PAE, comparing the proportion using McNemar's test. A p-value <0.05 for McNemar's test will be considered evidence that the proportion of AE's differs for medication, compared to PAE. A p-value >0.05 will be considered inconclusive. We will assume that the adverse events that occur following PAE will be attributed to the procedure and not medication.

We will present the percentage of prostate infarcted at 6 months and the incidence of minor complications at 1 month descriptively, and calculate 95% confidence intervals. Post-acquisition segmentation software will be used to measure infarct volume.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Registration Procedures

Study participants will be registered into REDCap®, a web based clinical research platform by one of the Study Coordinators.

9.3 Monitoring/Auditing

9.3.1 Data and Safety Monitoring Plan

Data and Safety Monitoring will be performed by a licensed physician who is not a study investigator.

The CRFs and any relevant source documents will be sent to the Study Monitor (as above) who will review them after treatment is complete for subjects 1, 10, 20 and 30.

Complications will be assessed by the co-PIs, categorized into major and minor categories and recorded on the CRF. CRFs and appropriate source documents will be made available to this individual for annually (every 12 months) review to ensure completeness of data collection. Any discrepancies will be immediately addressed by the co-PIs. All adverse events will be recorded and then summarized for inclusion in the final manuscript. Relatedness to the study

procedure will be assessed by an appropriately delegated investigator based on licensure.

Data monitoring will be performed by Study Monitor listed above. CRFs and appropriate source documents will be made available to this individual for bi-monthly review to ensure completeness of data collection. Any discrepancies will be immediately addressed by the co-PIs.

Because this is a small study with only 30 subjects, no DSMB will be used for this study. Data and safety monitoring will be conducted by an individual (Study Monitor) who is not an investigator on this study (see above).

9.3.2 Safety Monitoring

The research coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or safety monitor of all Unanticipated Problems/SAE's.

The research coordinator and co-principal investigators will confirm that all Adverse effects (AE) are correctly entered into the AE log by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; notify the IRB and FDA of all Unanticipated Problems/SAEs and AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The research coordinator will confirm that the AEs are correctly entered into the AE log. The Study Monitor will confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies, as required.

9.3.3 Monitoring Activities

A safety monitor who is not a study investigator (see section 9.3.1) will conduct safety monitoring after treatment is complete for subjects 1, 10, 20, and 30. Adverse events will be documented and reported as described above.

The following issues will be addressed quarterly or more frequently as necessary:

- Verify receipt of all documents and supplies needed to conduct study
- Informed consent obtained for each participant
- CRF completion
- Investigational product accountability
- Check and review of the regulatory binder and all essential documents
- Clinical supply inventory
- SAE reporting
- Enrollment issues and targets
- Protocol amendment and their approval by the IRB
- Significant protocol deviations
- Personnel changes

- Updated regulatory documentation
- Any other issue as deemed important to the conduct of the study

9.3.4 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Research Quality Assurance Office, IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

9.3.5 Study Closure

Upon study closure a final evaluation of the data will ensure that all forms are present and complete. Data will be maintained in a secure location for the appropriate duration as described in section 9.4.6. At the conclusion of this term, all forms will be shredded and destroyed.

9.4 Data Management

The online REDCap software system provided by UNC's TraCS Institute will be used for data collection and management, which will ensure that data collected are consistent and follow standardized coding. Data will be entered into REDCap by the study coordinator within 5 business days.

9.4.1 Data Quality

The study team will adhere to the Department of Radiology Internal Monitoring and Quality Assurance Standard Operating Procedures to ensure data quality is maintained for this study. The Department of Radiology's Internal Monitoring and Quality Assurance program will verify a random selection of at least 25% of all source documents for accuracy and completeness.

9.4.2 Missing Value Documentation

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Every attempt will be made to ensure that there is as little missing data as possible including reminder phone calls and follow-up phone calls, if a subject misses a

visit. If subjects withdraw, the reason for subject withdrawal will be documented in the study database.

9.4.3 Database Documentation

Copies of completed CRFs with subject IDs will be scanned and sent to the lead study coordinator at UNC for verification through the study database. All study data should be entered in REDCap within 5 business days to ensure timely entry.

9.4.4 Software

The online REDCap software system provided by UNC's TraCS Institute will be used for this study.

9.4.5 Documentation

The research coordinator will monitor the study files on a monthly basis to ensure the appropriate regulatory and IRB documentations are on file and up to date. The research coordinator will also be responsible for ensuring proper study documentation in order to verify compliance with Institutional policy, IRB, FDA and GCP guidelines in the following areas: Informed consent, Protocol, Source Documents and Electronic Case Report Forms.

The co-principal investigators and research coordinator will be responsible for maintaining IRB correspondence. IRB approved forms maintained, as part of the study will include the subject consent form and the HIPAA authorization form.

9.4.6 Data archival and data sharing

It is the investigators' responsibility to retain study essential documents during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Research records and original signed consent forms are to be retained by principal investigator for at least 6 years if the form includes authorization for use of private health information. Investigators may need to retain these documents for a longer period if required by an agreement with a sponsor or per other applicable regulatory requirements. The 6 year minimum retention of authorizations complies with the privacy regulation requirements.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC's IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, an IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

9.5.2 Protocol Deviations and Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems:

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study team using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study participants. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

10.0 PLANS FOR PUBLICATION

Study results will be submitted to a peer-reviewed journal for publication. This study will also be listed on Clinicaltrials.gov and study results will be posted in accordance with appropriate regulations and ICJME requirements.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study will be obligated to provide the sponsor with complete test results and all data derived from the study.

11.0 REFERENCES

1. Parsons JK. Benign Prostatic Hyperplasia and Male Lower Urinary Tract Symptoms: Epidemiology and Risk Factors. Current bladder dysfunction reports. 2010;5(4):212-8.
2. Reich O, Gratzke C, Bachmann A, Seitz M, Schlenker B, Hermanek P, et al. Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. The Journal of urology. 2008;180(1):246-9.
3. Uchida T, Ohori M, Soh S, Sato T, Iwamura M, Ao T, et al. Factors influencing morbidity in patients undergoing transurethral resection of the prostate. Urology. 1999;53(1):98-105.
4. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. European urology. 2013;64(1):118-40.
5. Kuntz RM, Lehrich K, Ahyai SA. Holmium laser enucleation of the prostate versus open prostatectomy for prostates greater than 100 grams: 5-year follow-up results of a randomised clinical trial. European urology. 2008;53(1):160-6.
6. Carnevale FC, Antunes AA. Prostatic Artery Embolization for Enlarged Prostates Due to Benign Prostatic Hyperplasia. How I Do It. Cardiovascular and interventional radiology. 2013.
7. Pisco JM, Rio Tinto H, Campos Pinheiro L, Bilhim T, Duarte M, Fernandes L, et al. Embolisation of prostatic arteries as treatment of moderate to severe lower urinary symptoms (LUTS) secondary to benign hyperplasia: results of short- and mid-term follow-up. European radiology. 2013;23(9):2561-72.
8. Laurent A, Beaujeux R, Wassef M, Rufenacht D, Boschetti E, Merland JJ. Trisacryl gelatin microspheres for therapeutic embolization, I: development and in vitro evaluation. AJNR American journal of neuroradiology. 1996;17(3):533-40.
9. Derdeyn CP, Graves VB, Salamat MS, Rappe A. Collagen-coated acrylic microspheres for embolotherapy: in vivo and in vitro characteristics. AJNR American journal of neuroradiology. 1997;18(4):647-53.
10. Pelage JP, Laurent A, Wassef M, Bonneau M, Germain D, Rymer R, et al. Uterine artery embolization in sheep: comparison of acute effects with polyvinyl alcohol particles and calibrated microspheres. Radiology. 2002;224(2):436-45.

11. Sun F, Sanchez FM, Crisostomo V, Diaz-Guemes I, Lopez-Sanchez C, Uson J, et al. Transarterial prostatic embolization: initial experience in a canine model. AJR American journal of roentgenology. 2011;197(2):495-501.
12. Sun F, Sanchez FM, Crisostomo V, Lima JR, Luis L, Garcia-Martinez V, et al. Benign prostatic hyperplasia: transcatheter arterial embolization as potential treatment--preliminary study in pigs. Radiology. 2008;246(3):783-9.
13. DeMeritt JS, Elmasri FF, Esposito MP, Rosenberg GS. Relief of Benign Prostatic Hyperplasia-related Bladder Outlet Obstruction after Transarterial Polyvinyl Alcohol Prostate Embolization. Journal of Vascular and Interventional Radiology. 2000;11(6):767-70.
14. Gratzke C, Schlenker B, Seitz M, Karl A, Hermanek P, Lack N, et al. Complications and early postoperative outcome after open prostatectomy in patients with benign prostatic enlargement: results of a prospective multicenter study. The Journal of urology. 2007;177(4):1419-22.
15. Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of Interventional Radiology clinical practice guidelines. Journal of vascular and interventional radiology : JVIR. 2003;14(9 Pt 2):S199-202.
16. Dasnurkar, A. (2015). Chronic Evaluation of HydroPearl in Porcine Model 30 Day End Point. Internal MicroVention report: unpublished.
17. Lepor H1, Williford WO, Barry MJ, Brawer MK, Dixon CM, Gormley G, Haakenson C, Machi M, Narayan P, Padley RJ. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. New England Journal of Medicine.1996 Aug 22; 335(8):533-9
18. Abt D, Hechelhammer L, Müllhaupt G, Markart S, Güsewell S, Kessler TM, Schmid HP, Engeler DS, Mordasini L. Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia: randomised, open label, non-inferiority trial. BMJ. 2018 Jun 19;361:k2338. doi: 10.1136/bmj.k2338.

12.0 APPENDICES

12.1 International Prostate Symptom Score (IPSS)

International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 Times	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

About the I-PSS

The International Prostate Symptom Score (I-PSS) is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 to 5. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic).

The questions refer to the following urinary symptoms:

Questions	Symptom
1	Incomplete emptying
2	Frequency
3	Intermittency
4	Urgency
5	Weak Stream
6	Straining
7	Nocturia

Question eight refers to the patient's perceived quality of life.

The first seven questions of the I-PSS are identical to the questions appearing on the American Urological Association (AUA) Symptom Index which currently categorizes symptoms as follows:

Mild (symptom score less than of equal to 7)
Moderate (symptom score range 8-19)
Severe (symptom score range 20-35)

The International Scientific Committee (SCI), under the patronage of the World Health Organization (WHO) and the International Union Against Cancer (UICC), recommends the use of only a single question to assess the quality of life. The answers to this question range from "delighted" to "terrible" or 0 to 6. Although this single question may or may not capture the global impact of benign prostatic hyperplasia (BPH) Symptoms or quality of life, it may serve as a valuable starting point for a doctor-patient conversation.

The SCI has agreed to use the symptom index for BPH, which has been developed by the AUA Measurement Committee, as the official worldwide symptoms assessment tool for patients suffering from prostatism.

The SCI recommends that physicians consider the following components for a basic diagnostic workup: history; physical exam; appropriate labs, such as U/A, creatine, etc.; and DRE or other evaluation to rule out prostate cancer.

12.2 Adverse Event Questionnaires

Prostatic Artery Embolization Study
IRB# PI:

Subject ID #:_____ Date of Visit: _____

Adverse Event

Have you experienced any of the following symptoms within the last month?

(Check all that apply)

- ☐ Nasal congestion
- ☐ Light headedness
- ☐ Retrograde ejaculation (Dry ejaculation)
- ☐ Priapism (Painful erection lasting 4 or more hours)
- ☐ Fatigue or weakness
- ☐ Headaches
- ☐ Hypotension (Low blood pressure)
- ☐ Heart fibrillation or Chest pain
- ☐ Swelling in hands, feet, or ankles
- ☐ Nausea
- ☐ Dizziness
- ☐ Fainting
- ☐ Erectile dysfunction
- ☐ Lower sex drive
- ☐ Gynecomastia (Male breast tissue)
- ☐ Dysuria (Burning with urination)
- ☐ Blood in Urine
- ☐ Blood in stool
- ☐ Blood in sperm
- ☐ Sores on penis
- ☐ Sores on buttocks

Form Completed By: _____

_____ _____

Signature Date