

<b>Protocol Title:</b>	<b>Prostate artery embolization for the treatment of symptomatic benign prostatic hyperplasia:</b>
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## 1. Introduction/Prior Investigation

Benign prostatic hyperplasia (BPH) produces symptoms in 50% of men over the age of 50 and 75% of men by age 70. Direct and indirect costs of BPH treatment in working age men are estimated to be \$3.9 billion yearly (1). Patients suffer with hesitancy, decreased urinary stream, intermittency, incomplete emptying, nocturia, frequency, and urgency. Patients with moderate to severe symptoms who fail medical management are often referred for transurethral resection of the prostate (TURP). The surgery is associated with complications in 5-15% of cases, including blood loss, UTI, urethral stricture, postoperative pain, incontinence or urinary retention, sexual dysfunction, and blood loss. Patients are typically hospitalized for 5 days (2).

Prostate artery embolization (PAE) was originally developed to treat hemorrhage after prostate biopsy or surgery. The procedure is modeled after uterine artery embolization (UAE) for the treatment of fibroids in women. Fibroid embolization is commonly performed at our institution and has been proven safe when compared to surgical management with a shorter hospital stay and quicker return to routine activity (3). In 2000, DeMeritt *et al* performed PAE to treat a patient with acute urinary retention and hematuria. After treatment, voiding improved and the prostate decreased in size 40% in 1 year (4). Animal studies show prostate size reduction after embolization with no major procedure related complications (5,6).

In the last 5 years, several studies from outside the United States demonstrated excellent technical and clinical success of PAE treating moderate to severe lower urinary tract symptoms (LUTS) due to BPH. These studies showed reduced prostate size and improved clinical symptoms scores after embolization with minimal side-effects. This resulted in Embosphere microspheres (Merit Medical; South Jordan, UT) receiving CE marking in Europe for PAE. The Society of Interventional Radiology (SIR) considers prostate artery embolization an emerging research priority and supports the performance of high-quality clinical research (7). The FDA recognizes this promising area of research and has published study guidelines for new device application with descriptions of patient selection and safety reporting (8).

The first study of PAE to treat BPH in humans was performed in 2010. Prostate volume reduction and clinical improvement was demonstrated in 2 patients with acute urinary retention (9). Pisco *et al* initially treated 15 patients with moderate to severe BPH and showed prostate volumes decreased 22% in 1 month with clinical severity score improved 6.7 points (10). They later published their expanded series of 255 patients with clinical success of 81.9% at 1 month, 75.2% at 1 year, and 72% at 2 and 3 years (11). Medium and long-term results were recently published in 630 patients with 81.9% and 76.3% cumulative success (12). The only major complication was a small area of bladder wall ischemia that required resection. Carnevale *et al* published the results of 11 patients treated with acute urinary retention treated with PAE. Clinical success was 91% with prostate volume decreased 30% after 1 year (13). There were no major complications or adverse events.

The first United States trial published in 2013 and updated in 2014 reports the treatment of 20 patients with symptomatic BPH. 90% technical success and 95% clinical success was reported at 1 month with prostate volume decreased 18% at 3 months (14). There were no major complications. Minor complications include a mild self-limited post-embolization syndrome consisting of pain, nausea, and malaise. Self-limited hematuria, dysuria, urinary frequency, and pelvic pain have also been reported. Gao *et al* published a prospective randomized trial comparing PAE to TURP in 114 patients (15). Both procedures demonstrated significant clinical improvement. The PAE group had more clinical failures (9.4% vs 3.9%) but reduced procedural bleeding, less need for urethral catheterization, and shorter hospital stay.

Prostate artery embolization has been performed with nonspherical PVA particles (10,11,12,15), tris-acryl gelatin microspheres (9,13), and hydrogel microspheres with a proprietary coating (14). No studies have been performed to directly compare the efficacy of these embolic agents. At UC San Diego we frequently

use microspheres for procedures requiring arterial embolization. We are experienced with a wide range of embolic materials. We propose using 300-500  $\mu\text{m}$  and 100-300  $\mu\text{m}$  Embospheres (Merit Medical; South Jordan, UT) as the embolic agent in this study.

PAE for LUTS attributed to BPH provides a minimally invasive treatment option with several advantages compared to surgical therapy. Excellent technical and clinical success is reported. The procedure is minimally invasive and can be performed as an outpatient procedure with minimal pain. Side effects are mild and self-limited, and major complications are rare. PAE is a technically challenging procedure. The clinical success rate is reduced when only unilateral embolization is possible, and poor technique could result in nontarget embolization resulting in pain or pelvic organ dysfunction. Further investigation is necessary to determine the safety of this procedure, the appropriate indications, the ideal embolic material, the durability of effect, and to directly compare this technique with surgical management.

## **2. Study Objectives**

### **2.1 Primary Objective**

The primary objective of this investigation is to evaluate improvement of benign prostatic hyperplasia (BPH) symptoms as assessed by the International Prostate Symptom Score (IPSS) after prostate artery embolization (PAE) with Embosphere® Microspheres in 20 patients with 24 months follow-up.

### **2.2 Secondary Objectives**

The secondary objectives of this investigation are to assess the following outcomes, compared to baseline values when appropriate:

1. PAE-related adverse events
2. Overall adverse events
3. Prostate volume as determined by transrectal ultrasound
4. Serum prostate specific antigen (PSA) level
5. Post void residual volume (PVR) as determined by transabdominal ultrasound
6. Post void residual urinary volume (PVR) as determined by uroflowmetry
7. Peak urine flow rate (Qmax) as determined by uroflowmetry
8. Sexual function as determined by the International Index of Erectile Function (IIEF)

### 3. Patient Population

#### 3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria in order to be eligible for this study.

1. Provided informed consent
2. Age greater than 50 years and less than 85 years
3. Prostate volume between 40 and 300 cm<sup>3</sup>
4. Diagnosis of BPH with moderate to severe lower urinary tract symptoms (LUTS) defined as at least one of the following:
  - a. IPSS greater than 18
  - b. IPSS Quality of Life (QoL) assessment greater than 3
  - c. Qmax less than 12 mL/sec
5. Refractory or intolerant to medical management
6. Ineligibility for or refusal of surgical management
7. One of the following criteria:
  - a. Baseline prostate specific antigen (PSA)  $\leq 2.5$  ng/mL
  - b. Baseline PSA  $> 2.5$  ng/mL and  $\leq 10$  ng/mL AND free PSA  $\geq 25\%$  of total PSA
  - c. Baseline PSA  $> 2.5$  ng/mL and  $\leq 10$  ng/mL AND free PSA  $< 25\%$  of total PSA AND negative 12 core prostate biopsy in the past 12 months
  - d. Baseline PSA  $> 10$  ng/mL AND negative 12 core biopsy within the past 12 months

#### 3.2 Exclusion Criteria

Patients that meet any of the following exclusion criteria will not be eligible for this study.

1. History of prostate, bladder or rectal malignancy. Biopsy proven urethral cancer.
2. History of rectal disease
3. Neurogenic bladder disorder due to multiple sclerosis, Parkinson's disease, spinal cord injury, diabetes, etc., as demonstrated on urodynamic testing.
4. Detrusor muscle failure, urethral stenosis, or urinary obstruction due to causes other than BPH, as demonstrated on urodynamic testing
5. Bladder diverticula greater than 5 cm or bladder stones greater than 2 cm
6. Cystolithiasis within the past three months
7. Baseline serum creatinine greater than 1.8
8. Evidence of tortuous or atherosclerotic blood vessels
9. Presence of collateral vessel pathways potentially endangering normal territories during embolization that cannot be bypassed with the microcatheter
10. Active urinary tract infection, interstitial cystitis, or prostatitis within the last 5 years
11. Coagulation disturbances not normalized by medical treatment
12. Allergy to iodinated contrast agents not responsive to steroid premedication regimen
13. Previous radical pelvic or rectal surgery, or pelvic irradiation
14. Prior surgical prostate intervention
15. Treatment with beta-blocker, antihistamine, anticonvulsant, or antispasmodic medication within 1 week of treatment UNLESS there has been a stable voiding pattern while medicated with the drug(s) for 6 months
16. Use of prostate active medications, including alpha blockers, anti-cholinergics, androgens, anti-androgens, gonadotropins-releasing hormonal analogs, PDE5-inhibitors, 5-alpha reductase inhibitors within 2 months of intervention, unless the medication is necessary to avoid symptom exacerbation and disability, in this case medication should not be initiated or dose adjusted within 1 month of study enrollment and dose should not be adjusted during the study period
17. Interest in future fertility
18. Mental condition or disorder that interferes with participants' ability to provide written informed consent

19. Current severe or uncontrolled disease (metabolic, hematologic, renal, hepatic, pulmonary, neurologic, cardiac, infectious or gastrointestinal) that in the Investigator's judgment makes the patient unsuitable for trial inclusion due to increased risk of complications
20. Known immunosuppression
21. Life expectancy less than 6 months

#### **4. Study Design**

This is a phase I/II, single center, prospective, single arm, investigational study to evaluate the safety and efficacy of prostate artery embolization (PAE) for treatment of severe lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) in patients with prostate size between 40 and 300 cm<sup>3</sup> that have either failed or are intolerant to medical management. Patients will be considered enrolled in the study once they have provided informed consent. A total of 20 patients will be enrolled in the single treatment arm of the study. Treated participants will be followed for no less than 24 months.

The study will involve a screening period in which patient eligibility is determined. Once eligibility is confirmed, patients will undergo PAE with Embosphere Microspheres within 4 weeks of baseline prostate ultrasound. Following treatment, patients will return for follow-up visits at 1, 6, 12, and 24 months post PAE. At each of these visits, patients will complete the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) questionnaires, undergo a physical exam, transrectal prostate ultrasound, transabdominal prostate ultrasound, uroflowmetry and laboratory evaluations, and medication and adverse event reviews.

The primary objective of the study will be improvement of BPH symptoms as assessed by the IPSS questionnaire. Patients will continue to be followed according to the institutional standard of care follow-up schedule after they complete the study.

Safety will be evaluated throughout the study by assessing adverse events and findings on physical examination. Concomitant medication usage will also be assessed.

## **5. Treatments and Assessments**

Study participants will be treated with a single PAE procedure performed with Embosphere Microspheres. The microspheres will be mixed with a contrast agent and will be delivered to the arteries supplying the prostate via a microcatheter. The occlusion endpoint will be stasis as defined as persistent contrast in the feeding vessel that persists for 5 heartbeats. A complete description of the technical protocol to be followed is provided in Appendix C.

After treatment with PAE, follow-up visits will take place at 1, 6 12, and 24 months,  $\pm 2$  weeks, from the day of treatment. A Schedule of Events and Study Flow Chart are provided in Appendices A and B, respectively. Cystoscopy and/or anoscopy will be performed for signs or symptoms of bowel or bladder injury, including hematuria, blood per rectum, or greater than expected pelvic pain at any time during the study protocol. Certain medical conditions, such as neurogenic bladder, detrusor failure, and urethral stenosis, may mimic LUTS due to BPH. Urodynamic testing will be obtained at baseline for patients with clinical symptoms or history concerning for these conditions.

### **5.1 Visit -1: Screening/Baseline (within 4 weeks of PAE)**

Patients meeting all of the inclusion and none of the exclusion criteria listed in Section 3 are eligible for participation in this study.

Prior to enrollment, each patient will have the following assessments performed:

- Obtain written informed consent
- Medical history, including demographics
- Physical exam including vital signs
- Recording of concurrent medical conditions
- IPSS and IIEF questionnaires
- Transrectal ultrasound (TRUS) of the prostate
- Transabdominal ultrasound (TAUS) of the bladder
- Uroflowmetry to assess Qmax
- Laboratory evaluations, including a complete blood count (CBC), complete metabolic panel (CMP), urinalysis, urine culture, and prostate specific antigen (PSA)
- Preprocedural CT angiography of the pelvis
- Prostate biopsy, if indicated by protocol
- Recording of concomitant medications
- Anoscopy if clinically indicated for evaluation of suspected rectal disease

### **5.2 Visit 1: Prostate Artery Embolization (PAE)**

The PAE procedure will be performed within 4 weeks of baseline prostate ultrasound. PAE with Embosphere Microspheres will be performed according to the technical procedure provided in Appendix C.

Treatment data recorded will include the following:

- Total fluoroscopy time
- Total radiation dose
- Number and origins of arterial supply
- Volume and size of embolic material delivered
- Evidence of collateral blood supply
- Duration of hospitalization
- Sedative medications administered
- Patient pain score before and after procedure

- Procedure adverse events

### **5.3 Visits 2, 3, 4: 1 Month, 6 Months, 12 Months (4 weeks, 24, 52 ± 2 weeks post PAE)**

Patients will have the following assessments performed:

- Physical exam, including vital signs
- IPSS and IIEF questionnaires
- TRUS of the prostate
- TAUS of the bladder
- Laboratory evaluations, including a complete blood count (CBC), complete metabolic panel (CMP), urinalysis, urine culture, and prostate specific antigen (PSA)
- Uroflowmetry to assess Qmax
- Cystoscopy, if clinically indicated
- Proctoscopy, if clinically indicated
- Review of concomitant medications and adverse events

Patients who are unable or unwilling to return for follow-up will be contacted by telephone, email, or mail to administer the IPSS and IIEF questionnaires, and to report any new treatments for BPH and/or LUTS.

### **5.4 Visit 5 (Long Term Follow-Up): 24 Months (104 ± 2 weeks post PAE)**

Patients will have the following assessments performed:

- Physical exam, including vital signs
- IPSS and IIEF questionnaires
- TRUS of the prostate
- TAUS of the bladder
- Laboratory evaluations, including a complete blood count (CBC), complete metabolic panel (CMP), urinalysis, urine culture, and prostate specific antigen (PSA)
- Uroflowmetry to assess Qmax

Patients who are unable or unwilling to return for follow-up will be contacted by telephone, email, or mail to administer the IPSS and IIEF questionnaires, and to report any new treatments for BPH and/or LUTS.

## **6. Withdrawal of Patients**

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patient from the study for any of the following reasons:

- Adverse event
- Concurrent medical condition
- Patient unwillingness to comply with study requirements
- Patient death
- Other Investigator decision

If a patient is withdrawn or discontinued from the study, the reason for withdrawal will be recording in the source documents and on the End of Study CRF. All patients withdrawn from the study will be encouraged to complete, if possible, all clinical evaluations scheduled for the 12 month follow-up visit. All adverse events will be followed as described in Section 7. Patients who are withdrawn from the study for any reason will not be replaced. The Principle Investigator may terminate the study at any time.

## 7. Adverse Events

### 7.1 Definitions

Adverse Event: An adverse event (AE) is any untoward medical occurrence in a patient, and does not necessarily have a causal relationship with the treatment. An AE therefore can be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicine or procedure, whether or not considered related to the product or procedure. A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for a serious adverse event as defined below.

Laboratory data will be collected as described in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

Patients will be instructed to report any AE that they experience to the Investigator or Study Coordinator. AEs will be assessed at each visit. AEs occurring during the clinical trial and the protocol-defined 12 month follow-up period will be recorded and reported on the AE CRF. In order to capture the most potentially relevant safety information during this study, the Investigator will record AE terms accurately and consistently throughout the study. Wherever possible, a specific disease or syndrome will be reported on the CRF rather than the associated signs and symptoms. If observed or reported signs or symptoms are not considered a component of a specific disease or syndrome by the Investigator they should be recorded as separate AEs on the AE CRF.

All adverse events will be assessed for severity, relationship to the study treatment, relationship to the study device, treatment required, and outcome/resolution. This information will be recorded and reported on the Adverse Event CRF (3500A).

Adverse events that might occur in this study include, but are not limited to:

- For cystoscopy and PAE: Burning sensation in the urethra, urinary infection, hematuria, pain
- General embolization risks: fever, hypotension, hypertension, arterial thrombosis and occlusion, pseudoaneurysm, risks of conscious sedation, amputation, and death.
- For PAE: Hematospermia, hemorrhage, injury to the bladder (including the bladder neck, ureteral orifice or trigone), impact on future fertility, vasospasm, rectorrhagia, inguinal hematoma, bladder/bladder neck ischemia and necrosis leading to bladder resection, balanitis, erectile dysfunction, rectal ischemia, rectal injury, allergic reaction to Embosphere Microspheres or contrast agent, radiation exposure, vascular perforation, need for subsequent surgery to repair non-target ischemia, and sensory abnormality

Serious Adverse Event: A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening, such that the patient was at immediate risk of death from the event as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form)
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospital admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that the patient's condition does not deteriorate in an unexpected manner during the study (e.g., surgical procedure performed earlier than planned)
- Results in persistent or significant disability/incapacity, such that the patient experiences a substantial disruption of their ability to conduct normal life functions

- Is an important medical event as determined by the Investigator. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms “serious” and “severe” since these are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as “serious,” which is based on event outcome or action criteria described above and is usually associated with events that pose a threat to a patient’s life or ability to function. A severe adverse event does not need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not constitute an SAE unless the patient is admitted to the hospital or the event meets any other criteria for seriousness. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the criteria described above. Seriousness (not severity) serves as a guide for defining regulatory reporting mechanisms.

Under this protocol, scheduled hospitalizations or elective surgical procedures will not be considered SAEs. Prolongation of a scheduled hospitalization will be considered an SAE as described above. Complications associated with surgical procedures or study treatments resulting in one of the outcomes above are considered SAEs.

## **7.2 Adverse Event Reporting**

The Investigators are responsible for monitoring the safety of patients who have been enrolled in this study. All AEs considered to be related to study treatment will be followed until the event resolves or has reached a fatal outcome. Adverse events will be evaluated for severity and graded following the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 as follows: Grade 1 (mild)- asymptomatic or mild symptoms; intervention not indicated, Grade 2 (moderate)- minimal symptoms; local or noninvasive intervention indicated, Grade 3 (severe)- medically significant but not immediately life threatening; hospitalization or prolonged hospitalization indicated, Grade 4 (life-threatening)- urgent intervention indicated, Grade 5- death related to AE.

The principle investigator will determine with attribution of each AE. AEs will be categorized into one of five classes: definite- clearly related to \_\_\_\_, probable- likely related to \_\_\_\_, possible- may be related to \_\_\_\_, unlikely- doubtfully related to \_\_\_\_, or unrelated- clearly not related to \_\_\_\_.

Attempts will be made to identify what the AE is related to and not merely what it is not related to.

The Investigators will document all AEs occurring during the study, commencing with the date of PAE treatment and including the protocol-defined post treatment follow-up period (21 CRF §312.64[b]), which is defined as 12 months post date of PAE, on the AE CRF. AEs and SAEs that occur following the signature of informed consent but prior to treatment will not be captured or reported.

The protocol will be terminated following the first occurrence of a serious adverse event, specifically nontarget pelvic embolization or procedure-related death.

### **7.3 Reporting Serious Adverse Events**

Any unanticipated adverse event or SAE, including death due to any cause that occurs during the study treatment or initial 12 month follow-up period, whether or not related to the study treatments, will be reported to the FDA within 3 days of the site learning of the event. The SAE form must be completely described on the AE CRF as well as the Serious Adverse Event form. Specifically, any bladder or rectal injuries will be reported to the IRB and FDA immediately.

Safety Contact Information:

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## **8. Symptom Assessments**

### **8.1 International Prostate Symptom Score (IPSS)**

The IPSS is a validated 8-question tool that is self-administered by the patient, and evaluates symptoms (7 questions) and quality of life (1 question). A copy of the IPSS can be found in Appendix D.

### **8.2 International Index of Erectile Function (IIEF)**

The IIEF is a validated 15-question tool that is self-administered by the patient, and evaluates male sexual function, sexual desire and intercourse satisfaction. A copy of the IIEF questionnaire can be found in Appendix E.

## **9. Statistical Analysis**

### **9.1 General Considerations**

In general, continuous variables will be summarized as n, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized as the number and percentage of patients in each category.

Data listings will include all data collected on the case report forms (CRFs), as well as any derived variables (study day, age, etc.). Data collected on patients who are screen failures will not be included in any summary tables, listings or analyses.

For each parameter, baseline is defined as the value reported prior to the study procedure. If multiple values were collected prior to the procedure, the value closest to the date/time of the initiation of the procedure will be used as baseline. This may include values collected earlier in the day on the date of the procedure.

Unscheduled data, such as information from unscheduled visits, repeat laboratory tests, or Investigator comments will be excluded from data listings and summary tables unless otherwise specified (such as data collected on adverse events). Any outliers detected during the review of the data will be investigated. If necessary, the data will be queried and corrected in the database prior to database lock and the generation of the final tables and listings.

All primary and secondary analyses will be performed on a locked database after all patients have completed the 12-month follow-up of the investigation or been lost to follow-up. Data from the long term follow-up period will be analyzed separately.

Analyses will be performed using SPSS, version 22 or higher.

### **9.2 Sample Size Calculations**

This is a phase I/II, single center, prospective, single arm, investigational study to evaluate the safety and efficacy of prostate artery embolization (PAE) for treatment of severe LUTS related to BPH in patients with prostate size between 40 and 300 cm<sup>3</sup> that have either failed or are intolerant to medical management. Twenty patients treated with PAE with Embosphere Microspheres are considered sufficient to provide data that will be used to evaluate the study objectives. No formal sample size calculations have been performed.

### **9.3 Analysis Populations**

#### **9.3.1 Intent-to-Treat Population**

The Intent-to-Treat (ITT) Population is defined as all patients who undergo PAE with Embosphere Microspheres. This will be the primary population for all efficacy analyses.

#### **9.3.2 Evaluable Population**

The Evaluable Population is defined as all patients who undergo PAE with Embosphere Microspheres, have valid IPSS data for the 12 month time point, and do not have any major protocol violations.

#### **9.3.3 Safety Population**

The Safety Population is defined as all patients who undergo PAE with Embosphere Microspheres. This is the same as the ITT Population.

### **9.4 Demographics and Baseline Characteristics**

Patient characteristics will be summarized for the ITT/Safety and Evaluable Populations, and will include the following:

- Patient demographics (age, race, ethnicity)

- Baseline BPH/LUTS characteristics (prostate size by TRUS, PSA, Qmax, PVR)
- Clinically significant medical history
- Concurrent medical conditions
- Prior BPH/LUTS therapy

## 9.5 Efficacy Analyses

All efficacy analyses will be based on the ITT Population on the locked database after all patients have completed the 12 month follow-up visit or are lost to follow-up. If <15% of patients are excluded from the Evaluable Population, only the analyses of the ITT Population will be presented in the summary tables. If >15% of patients are excluded from the Evaluable Population, secondary efficacy analyses of the primary efficacy outcome will be performed on the Evaluable Population and included in the summary tables.

### 9.5.1 International Prostate Symptom Score (IPSS)

The primary efficacy outcome will be based on the IPSS. The IPSS is a frequent used, validated, 8 item (7 symptom burden questions and 1 quality of life question) instrument which can be serially performed to compare the progression of symptoms and their severity over months and years. Patients are asked to assess how often they have experienced the following 7 symptoms in the past month: incomplete emptying, frequency, intermittency, urgency, weak urine stream, straining and nocturia. The response categories range from 0=Not at all to 5=Almost always. The total IPSS score is calculated by summing the responses for the 7 symptom burden items. The eighth item is an assessment of patient quality of life due to LUTS and does not contribute to the IPSS score calculation.

Patients will be classified into one of 3 symptom severity categories based on their total IPSS score as follows:

- Mildly symptomatic: 0-7
- Moderately symptomatic: 8-19
- Severely symptomatic: 20-35

The IPSS total score will be summarized for the baseline, 1 month, 6 month and 12 month time points, including change from baseline. Change from baseline will be calculated as post baseline IPSS score minus baseline IPSS score. A negative value indicates symptom improvement. 95% confidence intervals will be calculated for the mean change from baseline to the post baseline time points. For informational purposes, IPSS scores will also be summarized separately for patients that receive unilateral and bilateral PAE if there are sufficient numbers in both groups.

The primary efficacy analysis will be the change in IPSS total score from baseline to 12 months post PAE for the ITT population. A Paired-Sample Wilcoxon Signed Rank Test will be used to assess the statistical significance of the change from baseline to 12 months post PAE. A secondary analysis of the proportion of patients who have improved by at least one IPSS symptom category (i.e., severe to moderate, severe to mild, or moderate to mild) from baseline to 12 months post PAE will also be performed. A 95% confidence interval will be calculated for the proportion. The proportion of patients improving at least 3 points on the IPSS total score at the 12 month time point will also be summarized and the corresponding 95% confidence interval will be calculated.

The single IPSS quality of life item will be summarized separately for baseline and all post baseline time points. Change from baseline will be calculated, including the corresponding 95% confidence interval for the mean change at each time point.

### 9.5.2 Prostate Size

Prostate size in cm<sup>3</sup> as measured by TRUS will be summarized for the baseline, 1 month, 6 month and 12 month time points, including change and percent change from baseline. Change from baseline will be calculated as post baseline size minus baseline size. Percent change will be calculated as [change from baseline divided by baseline size] multiplied by 100. Negative changes from baseline indicate a decrease in

prostate size. The corresponding 95% confidence interval for the mean change and mean percent change will be presented for each time point.

#### **9.5.3 Peak Urine Flow Rate (Qmax)**

The Qmax determined by uroflowmetry will be summarized for the baseline, 1 month, 6 month and 12 month time points, including change from baseline. Change will be calculated as post baseline Qmax minus baseline Qmax. Positive values indicate an increase in flow rate. The corresponding 95% confidence interval for the mean change will be presented for each time point.

#### **9.5.4 Post Void Residual Urine Volume (PVR)**

The PVR determined by uroflowmetry will be summarized for the baseline, 1 month, 6 month and 12 month time points, including change from baseline. Change will be calculated as post baseline PVR minus baseline PVR. Negative values indicate a decrease in PVR. The corresponding 95% confidence interval for the mean change will be presented for each time point.

#### **9.5.5 International Index of Erectile Function (IIEF)**

The IIEF is a commonly used, validated instrument that consists of 15 items. Five subscales are calculated as follows:

- Erectile function (items 1-5, 15)
- Orgasmic function (9, 10)
- Sexual desire (11, 12)
- Intercourse satisfaction (6-8)
- Overall satisfaction (13, 14)

Each subscale will be summarized separately for the baseline, 1 month, 6 month and 12 month time points, including change from baseline. Change from baseline will be calculated as post baseline IIEF score minus baseline IIEF score. Positive values indicate an improvement in sexual function. 95% confidence intervals will be calculated for the mean change from baseline for each time point.

#### **9.5.6 Prostate Specific Antigen (PSA)**

PSA measured in ng/mL will be summarized for the baseline, 1 month, 6 month and 12 month time points, including change from baseline. Change will be calculated as post baseline PSA minus baseline PSA. Positive changes indicate a decrease in PSA values. The corresponding 95% confidence interval for the mean change will be presented for each time point.

#### **9.5.7 Handling of Missing and Spurious Efficacy Data**

All available data for treated patients will be included in the by-patient data listings and summary tables.

Obvious outliers for continuous data will be investigated and data queries will be generated as appropriate. If an outlier is determined to be a valid response, the summary analyses may be performed both including and excluding the outlier in order to evaluate the impact on the summary statistics. All outliers impacting the summary analyses will be discussed in the study report.

In the ITT analyses for the IPSS, IIEF, PSA and uroflowmetry variables, a Last Observation Carried Forward (LOCF) approach will be used. If a patient does not have any valid post-baseline data for a given outcome, the baseline value will be carried forward. This approach conservatively assumes there has been no improvement for those patients with completely missing post-baseline data. In addition, sensitivity analyses will be performed to determine the robustness of the ITT results using multiple imputation techniques if the data are determined to be missing at random.

#### **9.5.8 Adjustment for Multiplicity**

There will be no adjustment for multiplicity in this study.

## **9.6 Safety Analyses**

All safety analyses will be based on the Safety Population on the locked database after all patients have completed the 12 month follow-up visit or are lost to follow-up.

### **9.6.1 Adverse Events**

Safety summaries will include the incidence of treatment-emergent adverse events (TEAEs). TEAEs are defined as any adverse event (AE) that began on or after the date of treatment or worsened in severity or frequency after treatment was initiated. Events worsening in severity should be considered new AEs.

All TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summaries will present data by System Organ Class (SOC) and Preferred Term. TEAEs will be graded for severity into 1 of 5 classes following CTCAE version 4.0 criteria.

TEAEs will be summarized both based on the number of patients experiencing an event and as a summary of total number of TEAEs experienced by MedDRA, SOC, and Preferred Term.

A summary table will be created summarizing the number and percentage of patients with the following:

- At least one TEAE
- At least one severe TEAE
- At least one TEAE related to the study procedure or study device
- At least one treatment-emergent SAE
- At least one treatment-emergent SAE related to the study procedure or study device
- At least one TEAE leading to discontinuation of study participation
- At least one TEAE resulting in death

Separate summaries will be generated for the following types of TEAEs:

- Overall TEAEs
- Severe TEAEs
- TEAEs related to the study procedure or study device
- SAEs
- SAEs related to the study procedure or study device
- TEAEs resulting in death

### **9.6.2 Laboratory Evaluations**

All laboratory parameters will be presented in the data listings. All pre-treatment laboratory findings determined to be clinically significant by the Investigator will be reported as concurrent medical conditions. All clinically significant post treatment laboratory results will be reported as adverse events if they have worsened since baseline.

### **9.6.3 Vital Signs**

Vital sign data will be presented in the data listings. All pre-treatment vital signs determined to be clinically significant by the Investigator will be reported as concurrent medical conditions. All clinically significant post treatment vital sign results will be reported as adverse events if they have worsened since baseline.

### **9.6.4 Physical Examination Results**

Data from physical exams will be presented in the data listings. All pre-treatment physical exam findings determined to be clinically significant by the Investigator will be reported as concurrent medical conditions. All clinically significant findings on exams performed after treatment will be reported as adverse events if they have worsened since baseline.

### **9.6.5 Concomitant Medications**

Concomitant medications data will be presented in the data listings.

## **9.7 24 Month Follow-Up Data**

The data described in section 5.4 will be collected at the 24 month follow-up visit.

Data collected during the 24 month follow visit will be summarized separately from the data collected during the initial 12 month post PAE study period. All 24 month follow-up visit data recorded on the CRF will be included in the data listings. Select 24 month follow-up data may summarized, including change from baseline values, where applicable.

#### **10. Records, Confidentiality and Data Monitoring**

Each patient will be identified by study ID number only in the trial records. Study data will be recorded on pre-printed CRFs. Monitoring of study data recorded on source documents and reported on study CRFs will be conducted for all patients to ensure accuracy and completeness.

#### **11. Quality Control and Assurance**

It will be the responsibility of the Principal Investigator to ensure that data collection and reporting is complete and accurate.

#### **12. Good Clinical Practice**

This investigation will be conducted in accordance with the International Conference on Harmonization (ICH) E6 for Good Clinical Practice (GCP): Consolidated Guidance and all appropriate regulatory requirements. The Investigator will be thoroughly familiar with the appropriate use of the treatment procedure as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files will be established by the site personnel at the beginning of the study, maintained for the duration of the trial and retained according to all appropriate regulations.

#### **13. Ethical Considerations**

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Institutional Review Board (IRB) will review all appropriate study documentation, including the protocol, informed consent and any advertisements that will be used for the study, in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted once IRB approval has been obtained. Safety updates, annual progress reports and any revisions to these documents will be provided to the IRB by the Principal Investigator as required by regulations.

**14. Patient Information and Informed Consent**

After the study has been fully explained, written informed consent will be obtained from each patient prior to any study specific procedures being performed. The informed consent form will be approved by the IRB prior to use. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all other applicable regulatory requirements.

**15. Patient Confidentiality**

In order to maintain patient privacy, all CRFs, study reports and communications will identify the patient by their assigned study ID only. The patient's confidentiality will be maintained and will not be made publically available to the extent permitted by the applicable laws and regulations.

**16. Retention of Study Data**

University of California San Diego (UCSD) Medical Center will retain the written and/or electronic medical records, reports and data relating to the study in a secure location for a period of ten (10) years. UCSD Medical Center will prepare and maintain accurate written records of and data from the study.

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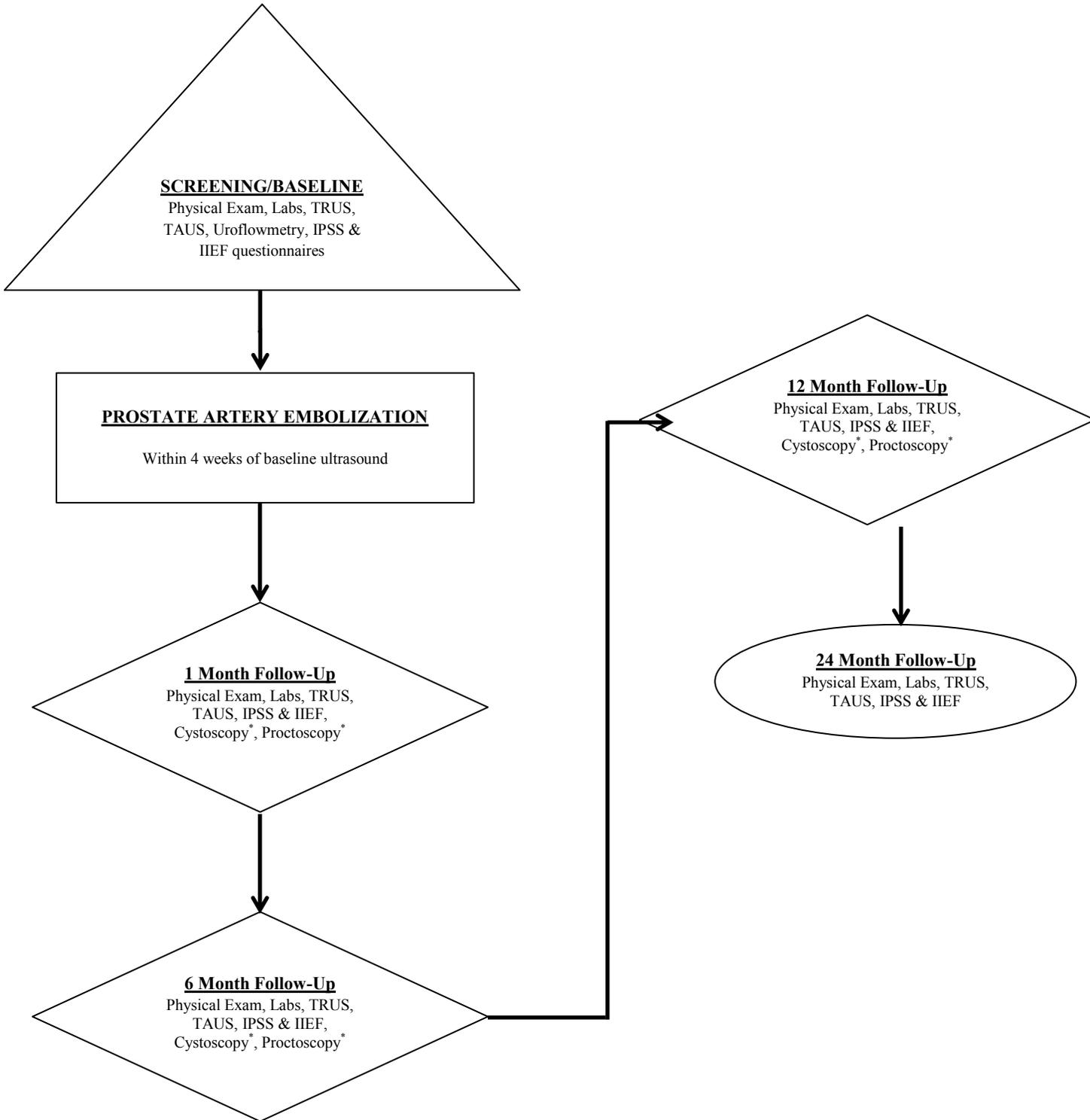
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## Appendix A: Schedule of Events

	Visit -1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening/ Baseline (within 4 weeks of Day 1)	Treatment (Day 1)	Month 1 (4 weeks ± 2 weeks)	Month 6 (24 weeks ±2 weeks)	Month 12 (52 weeks ± 2 weeks)	Month 24 (104 weeks ± 2 weeks)
Informed Consent	X					
Eligibility criteria assessment	X					
Demographics	X					
Transrectal Ultrasound	X		X	X	X	X
Transabdominal Ultrasound	X		X	X	X	X
Medical History	X					
Concurrent Medical Conditions	X					
Physical Examination	X		X	X	X	X
Vital signs	X		X	X	X	X
Blood tests	X		X	X	X	X
Urinalysis	X		X	X	X	X
PSA	X		X	X	X	X
IPSS	X		X	X	X	X
IIEF	X		X	X	X	X
Uroflowmetry	X		X	X	X	
PAE		X				
Cystoscopy			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	
Proctoscopy			X <sup>1</sup>	X <sup>1</sup>	X <sup>1</sup>	
Adverse Events		X	X	X	X	
Concomitant Medications	X	X	X	X	X	
Protocol violations	X	X	X	X	X	

<sup>1</sup> Cystoscopy and/or anoscopy will be performed for signs or symptoms of bowel or bladder injury, including hematuria, blood per rectum, or greater than expected pelvic pain at any time during the study protocol.

**Appendix B: Study Flow Chart**



\* Cystoscopy and/or anoscopy will be performed for signs or symptoms of bowel or bladder injury, including hematuria, blood per rectum, or greater than expected pelvic pain at any time during the study protocol.

## Appendix C: Technical Protocol for Prostate Artery Embolization

- Administer prophylactic IV antibiotics, based on institution standard of care. Choice of antibiotic and sedation will be at the discretion of the interventional radiologist.
- Prior to embolization, insert a Foley catheter into patient's bladder and fill it with a mixture of 50% contrast agent and 50% saline. This will provide a visual landmark during angiography.
- Local anesthesia should be administered for a transfemoral approach on the side with the best arterial pulse.
- Conduct pelvic angiography with a 5Fr catheter to evaluate aortoiliac vessels and prostate arteries during the arterial and late phases.
- Observe closely for vascular conditions and blood flow that might preclude catheter placement or embolic injection, including severe atheromatous disease, arteriovenous shunt, or presence of feeding arteries that are too small to accept the microspheres. If these conditions are present and a viable feeding artery without these problems cannot be identified, embolization will be conducted on the contralateral side of the prostate. If these conditions are present on both sides of the prostate, no embolization will be performed.
- If appropriate, anastomoses to non-targeted vessels and/or endangering collateral vessel pathways will be closed off with a larger size of embolic particles or embolic coils chosen to be appropriate to the size of the anastomosis or collateral vessel. If anastomoses or endangering collateral vessels cannot be closed off, the embolization will be performed only on the contralateral side of the prostate, if it is not affected by the condition. If anastomosis or endangering collateral vessels affects both sides of the prostate, no embolization will be performed.
- If vasospasm occurs, follow institution standard of care, which could include withdrawing the catheter slightly and waiting, or delivering a small amount of nitroglycerin. If the vasospasm cannot be resolved, conduct the embolization only on the contralateral side of the prostate.
- Ensure that the tip of the micro catheter is at or inside the ostium of the prostate arteries with additional angiography.
- Procedural endpoint is stasis of the terminal branches of the arteries feeding the prostate, while maintaining patency of the main artery branches.
  - Histopathology studies have demonstrated that intraprostatic vessels typically have diameters of approximately 300  $\mu\text{m}$ , so embolic particles of 300–500  $\mu\text{m}$  should be used unless an anatomic anomaly is identified.
- Embolize each of the prostate arteries to stasis without reflux of the mixture to undesired arteries. Stasis is defined as persistence of contrast in the target artery for 5 heartbeats.
- Perform follow up angiography after each vessel is embolized to evaluate prostate devascularization and to identify any remaining collateral blood supply to the prostate. All feeding vessels should be embolized.
- When all apparent vessels feeding one side of the prostate are embolized, embolize the other side using the same technique.
- Once the embolization procedure is complete, follow institution's standard of care for catheter and introducer removal and closure of femoral puncture.
- It is suggested to leave the Foley catheter in place for at least 6 hours after procedure. Catheter removal time is at the discretion of the interventional radiologist. After catheter removal PVR will be checked after spontaneous voiding and patients discharged for PVR<250. Otherwise Urology will be contacted for further management.
- It is suggested that patients be discharged with non-opioid analgesic, NSAID, omeprazole and antibiotics for 7 days.

**Potential Risks Associated with PAE:**

Adverse events that might occur in this study include, but are not limited to:

- For cystoscopy and PAE: Burning sensation in the urethra, urinary infection, hematuria, pain
- General embolization risks: fever, hypotension, hypertension, arterial thrombosis and occlusion, pseudoaneurysm, risks of conscious sedation, amputation, radiodermatitis and death.
- For PAE: Hematospermia, hemorrhage, injury to the bladder (including the bladder neck, ureteral orifice or trigone), impact on future fertility, vasospasm, rectorrhagia, inguinal hematoma, bladder/bladder neck ischemia and necrosis leading to bladder resection, balanitis, erectile dysfunction, rectal ischemia, rectal injury, allergic reaction to Embosphere Microspheres or contrast agent, radiation exposure, vascular perforation, need for subsequent surgery to repair non-target ischemia, and sensory abnormality

The risk of radiation dermatitis will be mitigated by following the standard principles of radiation dose reduction employed in our fluoroscopy laboratory protocols and Interventional Radiology society standards. This includes, but is not limited to, following ALARA principles, monitoring and limiting fluoroscopy time and dose, reducing frame rates when possible, utilizing last-image hold, optimal collimation, reducing magnification, and optimizing imaging geometry. Radiation entry site will be varied as possible to reduce skin entrance doses.

**See Embosphere Microsphere IFU for complete product information.**

**Warnings on the IFU include:**

- Embosphere Microspheres do not form aggregates, and as a result, penetrate deeper into the vasculature compared to similar size PVA particles.
- Some Embosphere Microspheres may be slightly outside of the labeled range so the physician should carefully select the size of Embosphere Microspheres according to the size of the target vessels at the desired level of occlusion in the vasculature after consideration of the arteriovenous angiographic appearance.
- Serious radiation induced skin injury may occur to the patient due to long periods of fluoroscopic exposure, large patient diameter, angled x-ray projections, and multiple image runs.
- Careful consideration should be given whenever use is contemplated of embolic agents that are smaller in diameter than the resolution capability of your imaging equipment. The presence of arteriovenous anastomoses, branch vessels leading away from the target area or emergent vessels not evident prior to embolization can lead to mistargeted embolization and severe complications.

## Appendix D: International Prostate Symptom Score (IPSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	YOUR SCORE
<b>Incomplete emptying</b> Over the past 4 weeks, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
<b>Frequency</b> Over the past 4 weeks, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
<b>Intermittency</b> Over the past 4 weeks, how often have you found you stopped and started again several times when you urinate?	0	1	2	3	4	5	
<b>Urgency</b> Over the past 4 weeks, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
<b>Weak stream</b> Over the past 4 weeks, how often have you had a weak urinary stream?	0	1	2	3	4	5	
<b>Straining</b> Over the past 4 weeks, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 or More Times	
<b>Nocturia</b> Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	
<b>IPSS Total Score</b>	0-7=Mildly symptomatic, 8-19=Moderately symptomatic, 20-35=Severely symptomatic						
	Delighted	Pleased	Mostly Satisfied	Mixed – almost equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
<b>Quality of life due to urinary symptoms:</b> If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

## Appendix E: International Index of Erectile Function (IIEF)

INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF) QUESTIONNAIRE						
<i>Please circle the appropriate number to respond to each question.</i>						
	0	1	2	3	4	5
1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?	No sexual activity	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always
2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?	No sexual activity	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always
3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	Did not attempt intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always
4. Over the past 4 weeks, during sexual intercourse, <u>how often</u> were you able to maintain your erection after you had penetrated (entered) your partner?	Did not attempt intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always
5. Over the past 4 weeks, during sexual intercourse, <u>how difficult</u> was it to maintain your erection to completion of intercourse?	Did not attempt intercourse	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
6. Over the past 4 weeks, how many times have you attempted sexual intercourse?	No attempts	One to two attempts	Three to four attempts	Five to six attempts	Seven to ten attempts	Eleven plus attempts
7. Over the past 4 weeks, when you attempted sexual intercourse, how often was it satisfactory to you?	Did not attempt intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always
8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?	No intercourse	No enjoyment	Not very enjoyable	Fairly enjoyable	Highly enjoyable	Very highly enjoyable
9. Over the past 4 weeks, when you had sexual stimulation <u>or</u> intercourse, how often did you ejaculate?	No sexual stimulation / intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always

**INTERNATIONAL INDEX OF ERECTILE FUNCTION (IIEF) QUESTIONNAIRE**

*Please circle the appropriate number to respond to each question.*

	0	1	2	3	4	5
<b>10. Over the past 4 weeks, when you had sexual stimulation <u>or</u> intercourse, how often did you have the feeling of orgasm or climax?</b>	No sexual stimulation / intercourse	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always
<b>11. Over the past 4 weeks, how often have you felt sexual desire?</b>		Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost Always/ Always
<b>12. Over the past 4 weeks, How would you rate your level of sexual desire?</b>		Very low / none at all	Low	Moderate	High	Very high
<b>13. Over the past 4 weeks, how satisfied have you been with your overall <u>sex life</u>?</b>		Very dissatisfied	Moderately dissatisfied	About equally satisfied and dissatisfied	Moderately satisfied	Very satisfied
<b>14. Over the past 4 weeks, how satisfied have you been with your <u>sexual relationship</u> with your partner?</b>		Very dissatisfied	Moderately dissatisfied	About equally satisfied and dissatisfied	Moderately satisfied	Very satisfied
<b>15. Over the past 4 weeks, how do you rate your <u>confidence</u> that you could get and keep an erection?</b>		Very low	Low	Moderate	High	Very high