Protocol Title: PROSPECTIVE, CONTROLLED INVESTIGATION OF PROSTATE ARTERY EMBOLIZATION WITH EMBOSPHERE® MICROSPHERES COMPARED TO TRANSURETHRAL RESECTION OF THE PROSTATE FOR THE TREATMENT OF SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA

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1 Introduction

1.1 Background:

Benign Prostatic Hyperplasia

The prostate is a walnut-sized gland that forms part of the male reproductive system. The gland is made of two lobes, or regions, enclosed by an outer layer of tissue. The prostate continues to grow during most of a man's life, but the enlargement does not usually cause problems until after age 50. Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in men, with more than 50% of men in their sixties and as many as 90% in their seventies and eighties having some symptoms of BPH. As life expectancy increases, so does the occurrence of BPH. In the United States in 2000, there were 4.5 million visits to physicians for BPH in the US with a direct cost of $1.1 billion. (NIDDK; Wei 2005)

As the prostate enlarges, the layer of tissue surrounding it stops it from expanding, causing the gland to press against the urethra like a clamp. The bladder wall becomes thickened and irritable, and begins to contract even when it contains small amounts of urine, causing more frequent urination. Eventually, the bladder weakens and loses the ability to empty itself, so some of the urine remains after voiding. In addition, the prostate can push upward against the bladder floor, contributing to bladder outlet obstruction. The narrowing of the urethra and partial emptying of the bladder cause many of the problems associated with BPH. Lower urinary tract symptoms (LUTS) are common complaints resulting from BPH, and approximately half of all men with a histologic diagnosis of BPH have moderate to severe LUTS. Symptoms include nocturia, urinary frequency, urgency, decreased urine flow rates, hesitancy and incomplete bladder emptying. Over time, urine retention may cause an increase in urinary tract infections, bladder or kidney damage, bladder stones, or incontinence. (NIDDK , Wei 2005)

Current Treatment of BPH

Medical treatment is usually the first line therapy for LUTS due to BPH. The two main categories of medications for management of BPH are alpha blockers and 5α -reductase inhibitors. Alpha blockers (α_1-adrenergic receptor antagonists) are the most common choice for initial therapy. Alpha blockers used for BPH include doxazosin, terazosin, alfuzosin, tamsulosin, and silodosin. They work by relaxing smooth muscle in the prostate and the bladder neck, thereby decreasing the hindrance to urine flow. Common side effects of alpha blockers include orthostatic hypotension, ejaculation changes, loss of libido, impotence, nasal congestion, and weakness. Men planning on undergoing cataract surgery are not good candidates for alpha blocker therapy because it can result in intraoperative floppy iris syndrome (IFIS). IFIS occurs in 43-90% of men taking tamsulosin.

The 5α-reductase inhibitors include finasteride and dutasteride. These medications inhibit 5a-reductase, which reduces production of DHT, one of the hormones responsible for enlarging the prostate. Side effects include decreased libido and ejaculatory or erectile dysfunction. Because they have different mechanisms of action, the two medications are sometimes used together. (Kacker 2011; McVary 2011)

Patients who cannot tolerate these drugs or are refractory to treatment typically receive surgery or a minimally invasive therapy. In general, transurethral resection of the prostate (TURP) is still considered the gold standard of prostate interventions for patients that require a procedure. The procedure involves removing part of the prostate through the urethra with a resectoscope. The resectoscope uses an electrical loop to cut tissue and seal blood vessels. The most common adverse event is retrograde ejaculation, occurring in up to 65% of patients, followed by hemorrhage requiring transfusion (8%), erectile dysfunction (6.5%) urethral stricture (4%), and incontinence (2%). (Kacker 2011; McVary 2011)

There are also a number of less invasive methods for reducing prostate size, including radiofrequency, microwave and laser therapies. All of these treatment methods involve introducing energy into the body and urethral access and manipulation.

Photoselective vaporization prostatectomy (PVP), also known as GreenLight Laser, vaporizes prostate tissue through selective absorption by hemoglobin, which creates a TURP-like defect. A major advantage of PVP is that it causes coagulation during tissue vaporization so the method can be used for patients on anticoagulation therapy, and it is also viable for patients with acute urinary retention. Postoperative irritative voiding symptoms, including urge incontinence, are common, with an incidence over 25%, and retrograde ejaculation occurs in approximately 50% of patients.

Transurethral radiofrequency needle ablation (TUNA) consists of endoscopes with attached needles that are inserted into the prostate to emit low-level radiofrequency energy to induce necrosis. The dead tissue is absorbed back into the prostate, partially reducing its size. The most frequent adverse events from TUNA are hematuria and urinary retention, but they are usually transitory. The limitation of this treatment is that the amount of prostate reduction is less than with some other treatments, and there is a trend toward decreased urinary improvement after 3 years.

Transurethral microwave thermotherapy (TUMT), similar to TUNA, uses heat to ablate tissue to reduce the size of the prostate. Instead of utilizing needles, TUMT employs a microwave antenna placed on the end of a urethral catheter to deliver the treatment. Some, but not all, models employ urethral cooling mechanisms to protect the urethra, bladder neck and sphincter from damage. Contraindications for use include implanted pacemakers, defibrillators, metallic implants, and “ball valve” median lobe enlargement. Chronic urinary retention is a relative

contraindication. Variations in procedure, the difference between high versus low energy level models and transurethral versus transrectal methods have led to varying results. Postoperative dysuria has been reported in up to 50% of patients treated with this method, and in 2000 the FDA warned against rare but severe complications such as penile necrosis and fistula.

Holmium lasers initially were used for tissue ablation (HoLAP), but holmium enucleation of the prostate (HoLEP) became possible with the advent of mechanical morcellators. The laser wavelength is absorbed by water and produces vaporization of prostate tissue. Instead of ablating the tissue, the laser cuts off a portion of the prostate, which is then cut into smaller pieces by the morcellator and flushed out with irrigation fluid. It can be used for prostates as large as 300gm. There is little bleeding during or after the procedure, but the technical learning curve is high, which can result in capsular perforations, strictures and conversions to surgery. (Kacker 2011; McVary 2011)

All these technologies have the same objective—to remove prostate tissue to relieve constriction of the urethra or bladder outlet obstruction and reduce symptoms of LUTS. They produce outcomes similar to TURP, although there is not as much data on long term effectiveness as there is for surgery. The challenge for developing new methods of treating symptomatic BPH is to reduce hyperplastic tissue and achieve good long term control of LUTS while reducing adverse events and negative impacts on quality of life, such as ejaculatory disorders.

1.2 Prostate Artery Embolization (PAE)

Embolization of prostate arteries has been used for many years to control serious bleeding after biopsy or prostatectomy. The first published case in which it was recognized that embolization could have a therapeutic affect on benign prostatic hyperplasia (BPH) was by DeMeritt and colleagues (DeMeritt 2000). The paper reported on a patient with BPH who had such severe hematuria that he required transfusion, and who underwent prostate artery embolization with PVA particles in an attempt to stop the bleeding. As intended, the bleeding stopped immediately after embolization. Unexpectedly, the physicians found that the prostate size had reduce to 52% and 62% of its pre-embolization size at follow up visits 5 and 12 months later. This case was the first indication that prostate artery embolization (PAE) could be clinically effective in the treatment of BPH. (DeMeritt 2000)

More recently there have been two studies in peer-reviewed journals of investigations of PAE using Embosphere Microspheres in animal models, and one published abstract.

The first investigation, by Faintuch and colleagues (Faintuch SIR 2008) involved embolization of 6 beagles with Embosphere Microspheres. Immediately following embolization retrograde urethrocystography and multiphasic, multislice, contrast enhanced CT scans were obtained to document distribution of the microspheres, perfusion, and 3D volume analysis.

CTs done 1 month after treatment demonstrated good distribution of the microspheres in the embolized territory with no evidence of non-targeted embolization. All animals who received bilateral PAE showed improvement in the degree of stenosis of their prostatic urethras, and dogs who underwent either unilateral or bilateral PAE displayed decreased perfusion, cavitary necrosis and volume reduction of the prostate, with excellent histopathological and radiological correlation.

Soon after Sun and colleagues (Sun 2008) published a study in which they used 16 healthy pigs to evaluate the technical feasibility and safety of PAE. All animals had selective angiography, and half then underwent embolization with Embosphere Microspheres. Three months post treatment the investigators evaluated the sexual function of the pigs during mating. Subsequently the animals were euthanized and their prostates were examined for size and histopathological appearance.

The prostate artery embolization was technically successful in all eight animals without complications. No significant difference in sexual desire or function was noted between the two groups ($p=0.328$). After sacrifice, the mean prostate volume of the treated animals was statistically significantly smaller than that of the control group ($p<0.001$) and histopathological exam demonstrated that the Embosphere Microspheres had occluded the arterioles of the prostate. This resulted in disappearance of tissue in the surrounding area and atrophy of residual glandular tissue. Examination of the bladder, ureters , urethra, sigmoid colon, and rectum revealed no abnormalities.

Sun and colleagues also evaluated pathologic responses and technical safety of PAE in a canine model (Sun 2011). In this study 10 beagles were surgically castrated and given hormone therapy for 4 months to induce BPH. After 3 months of hormone administration all dogs had selective angiography and 7 underwent PAE with Embosphere Microspheres, with the other 3 acting as controls. One month later all dogs were sacrificed.

MRI and transrectal ultrasound demonstrated that all 10 dogs developed BPH from the hormone therapy. The prostates of all 7 dogs that had been embolized exhibited an intraprostatic cavity one month after PAE, and of these, 4 animals demonstrated significant shrinkage in size. Of the 3 embolized dogs that had an increase in prostate size, imaging and necropsy revealed huge cavities occupying 90-100% of the entire prostate. The prostates of the control animals displayed no cavitary necrosis. There were no complications associated with the PAEs. Upon histopathological examination, the ureters, seminal vesicles, deferent ducts, bladder, urethra and sigmoid colon were intact in all dogs. No necrosis was found in these tissues.

The first intentional treatment of BPH with PAE in humans was done by Carnevale and colleagues (Carnevale 2010). They performed PAE for 2 patients with acute urinary retention due to BPH who were refractory to treatment with selective α-blockers, were being managed with long term indwelling catheters, and were waiting for surgery. Prior to embolization patients

were assessed using digital rectal examination, urodynamic testing, prostate biopsy, transrectal ultrasound (TRUS) and MRI. Malignancy and non-BPH causes of urinary obstruction were ruled out. Post treatment with embolization the patients had repeat urodynamic testing, TRUS and MRI at 30, 90 and 180 day follow up visits.

The 2 patients underwent angiography and embolization with Embosphere Microspheres under local anesthesia. The first patient, aged 67 with a history of hypertension, had a prostate estimated at 63gm by TRUS and 69gm by MRI with an intravesical prostate protrusion (IPP) of 9mm. Bilateral PAE was performed successfully without complications.

The patient experienced mild retropubic pain for 24 hours, which was treated with non-opioid analgesics. He had no fever or hematuria and was discharged 3 days after PAE. The patient was able to urinate spontaneously when his catheter was removed 15 days after embolization. One month later at follow up his prostate was reduced by 33.3% and 39.1% by TRUS and MRI respectively, IPP was reduced to 4mm, and post void residual urine (PVR) volume was 8ml. At 3 months post treatment the patient was urinating normally. The IPP was the same, but PVR was reduced to 5ml and the prostate size reduction was 39.7% and 44.9% by TRUS and MRI respectively. During the 6 month evaluation PVR was absent and prostate size was similar to that at 3 months.

The second patient was aged 68 years, with a history of atrial fibrillation and hypertension. TRUS showed a prostate of 51gm and asymmetric hypertrophy of the right lobe, with an IPP of 16mm. Prostate size was 54gm by MRI, and showed a discrete 1.1 cm avascular cystic node on the right, protruding at the bladder neck. Unilateral PAE of the right prostate arteries only was done because the left arteries could not be visualized.

The patient had no post PAE symptoms, was discharged 3 days after treatment, and was able to urinate spontaneously when the catheter was removed 10 days after embolization. At 1 month the patient reported some episodes of nocturia. PVR was 110ml and IPP had not changed from baseline at 16mm, but prostate size was reduced 16.9% and 24.1% by TRUS and MRI respectively. MRI showed that the avascular nodule had increased from 1.1cm at baseline to 1.3cm. By the 3 month follow up visit the patient was voiding normally. IPP continued at 16mm, but PVR was reduced to 68ml and size reduction was 25.5% and 27.8% by TRUS and MRI. The avascular area on the right persisted. The patient's condition was similar at 6 month follow up.

For both patients urine stream increased with time, accompanied by reduction of PVR and prostate size shrinkage that was sustained at 6 months. Reduction was greater in the patient who received bilateral embolization.

The same investigators published midterm follow up data for these 2 patients (Carnevale 2011). The prostate of the first patient, who had had bilateral PAE, continued to decrease in size over

time, with a reduction of 53.6% by MRI at 18 month follow up, compared with 47.8% at 6 months. The patient was continuing to void normally 30 months post embolization.

The second patient, for whom it had only been possible to do unilateral PAE due to prostate arteries on the left not being visualized during angiography, demonstrated an increase in prostate size at 18 months compared to imaging done at the 6 month follow up visit. MRI showed a 12.2% reduction from baseline at 18 months compared to 27.8% at 6 months. PVR had increased to 200 ml and IPP was 17mm compared to 85ml and 15mm respectively at 6 months, but at both the 18 and 30 month visits the patient was continuing to void normally.

Most recently Carnevale presented outcomes of 40 embolizations (Carnevale GEST 2012). Eleven patients with acute urinary retention treated with indwelling catheters were enrolled in a Phase I/II study and treated with PAE. This group includes the first 2 feasibility cases (Phase I, discussed earlier) plus 9 other patients (Phase II). After completion of this study 28 additional patients were treated. Evaluations at baseline, 1, 3, 6, and 12 months were done by MRI, TRUS, urodynamic testing (baseline and every 12 months), PSA, IPSS and IIEF. Embolization was done with Embosphere Microspheres under local anesthesia. Clinical success was achieved in 10 of the 11 phase I/II patients (91%), with patients able to urinate spontaneously after catheter removal and no recurrence of LUTS symptoms during 16-45 months of follow up. The single clinical failure was a patient who was embolized twice, but still was not able to urinate spontaneously. He was referred to surgery and treated by TURP. Minor adverse events included diarrhea, light rectal bleeding (2-3 tsp), hematuria, anal burning sensation, retropubic pain and dysuria. Only non-opioid pain medications were needed for management. One case of bladder ischemia was recognized retrospectively. The patient experienced no pain or urinary retention but a defect was seen in the bladder wall by MRI during follow up at 30 days. This resolved spontaneously, and was not seen at future MRI surveillance. No treatment was required.

Average PSA levels dropped from 10.1ng/ml at baseline to 3.5ng/ml at month 3 ($p=0.003$), average prostate size reduction was approximately 30% by MRI ($p=0.002$) and TRUS ($p=0.004$). It was not possible to obtain IPSS and IIEF scores at baseline because all these patients had indwelling catheters prior to PAE, but these scores improved from first measurement at 30 days post treatment throughout a year of follow up, with the IPSS being statistically significant ($p=0.04$). Average response from the quality of life question of the IPSS went from 6 (terrible) at baseline to 1.1 (pleased) at the 30 day follow up, and continued at <1 (delighted) from 3-12 months of follow up. Urodynamic test results also demonstrated marked improvement. Average changes from baseline to 12 months were as follows: urine flow (Qmax) improved from 4.2ml/sec to 10.8ml/sec ($p=0.009$), detrusor muscle pressure (Pdet) reduced from 85.7 to 51.5 ($p=0.007$) and PVR decreased from 160.6ml to 60.0ml ($p=0.04$).

In the subsequent patients without acute urinary retention or indwelling catheters at time of treatment, average IPSS scores decreased from 20.3 at baseline (severe) to 1.7 at 90 days (mild),

and prostate size reduction averaged 26.4% by MRI in the same time period. Urodynamic test results were also notable in this group: Qmax increased from an average 8.0ml/sec at baseline to 17.4ml/sec at 90 days. Overall clinical success for all 39 patients, defined as LUTS improvement and ability to urinate spontaneously was 97.5%.

These encouraging clinical outcomes with low risk profile have led to the development of this comparative study.

2 Study Objectives

2.1 Primary Objective

The primary study objective is to evaluate improvement of symptoms from benign prostatic hyperplasia (BPH) as assessed by the International Prostate Symptom Score (IPSS) for prostatic artery embolization (PAE) with Embosphere® Microspheres compared with conventional transurethral resection of the prostate (TURP).

2.2 Secondary Objectives

The key secondary objectives are to assess the outcomes listed below and compare the findings for patients treated with PAE and TURP.

- Duration of hospitalization post procedure
- Duration of post procedure catheterization

Additional secondary objectives are to assess the outcomes listed below and to compare the findings for patients treated with PAE and TURP.

- Change from baseline in peak urine flow rate (Qmax)
- Change from baseline in post-void residual urinary volume (PVR)
- Change from baseline in erectile function using the International Index of Erectile Function (IIEF)
- Change from baseline in mean prostate volume, as determined by MRI
- Change from baseline in prostate specific antigen (PSA)
- Overall adverse events

- Procedure related adverse events

3 Patient Population

3.1 Inclusion Criteria:

Patients must meet all of the following inclusion criteria in order to be entered into the study:

1. Patient is age 50 to 79, inclusive
2. Patient has signed informed consent
3. Patient has had lower urinary tract symptoms (LUTS) secondary to BPH for at least 6 months prior to study treatment
4. Patient has a baseline IPSS Score $\geq$ 13 at baseline
5. Patient has a prostate size of at least 50 grams and not more than 90 grams, measured by MRI
6. Patient has BPH symptoms refractory to medical treatment or for whom medication is contraindicated, not tolerated or refused
7. Patient must be a candidate for TURP
8. Patient must meet ONE of the following criteria:
    - Baseline Prostate Specific Antigen (PSA) $\leq$2.5 ng/mL (no prostate biopsy required)
    - Baseline PSA >2.5 ng/mL and $\leq$10 ng/mL AND free PSA $\geq$ 25% of total PSA (no prostate biopsy required)
    - Baseline PSA >2.5 ng/mL and $\leq$10 ng/mL AND free PSA < 25% of total PSA AND a negative prostate biopsy result (minimum 12 core biopsy) within the prior 12 months
    - Baseline PSA >10 ng/mL AND a negative prostate biopsy (minimum 12 core biopsy) within the prior 12 months

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria may not be entered into the study:

1. Active urinary tract infection

2. Biopsy proven prostate or bladder cancer, or any cancer other than basal or squamous cell skin cancer
    - The following patients must have undergone prostate biopsy with a minimum of 12 cores and have had a negative histopathology report within the prior 12 months to be enrolled in the study:
        - Patients with DRE findings suspicious for prostate cancer
        - Patients with baseline PSA levels > 10 ng/mL
        - Patients with baseline PSA levels >2.5 ng/mL and ≤ 10ng/mL AND free PSA < 25% of total PSA
    - Patients with cystoscopy findings suspicious for bladder cancer must undergo biopsy and have a negative histopathology report to be enrolled in the study

3. Bladder atonia, neurogenic bladder disorder or other neurological disorder that is impacting bladder function (eg multiple sclerosis, Parkinson's disease, spinal cord injuries, etc)

4. Urethral stricture, bladder neck contracture, sphincter abnormalities, urinary obstruction due to causes other than BPH, or other potentially confounding bladder or urethral disease or condition

5. Patient has taken beta blockers, antihistamines, anticonvulsants, or antispasmodics within 1 week of study treatment AND has **not** been on the same drug dosage for 6 months with a stable voiding pattern
    - Dosage of these medications should not change during study participation unless medically necessary

6. Patient has taken antidepressants, anticholinergics, androgens or gonadotropin-releasing hormonal analogues within 2 months of study treatment AND has **not** been on the same drug dosage for at least 3 months with a stable voiding pattern

7. Patient has taken 5-alpha reductase inhibitors or alpha blockers within 1 month of study treatment AND has **not** been on the same drug dosage for at least 3 months with a stable voiding pattern

8. Previous non-medical BPH treatment, including surgery, TURP, needle ablation, microwave or laser therapy, balloon dilation, stent implantation, or any other invasive treatment to the prostate

9. Any known condition that limits catheter-based intervention or is a contraindication to embolization, such as intolerance to a vessel occlusion procedure or severe atherosclerosis.

10. Patient is unable to stop taking anticoagulant, NSAID or anti-platelet therapy for 7 days prior to study treatment

11. Unable to have MRI imaging (eg metal implant including pacemaker, replacement joint, etc)

12. Patient has an asymmetric prostate, with $\geq$ 20% difference in size between lobes

13. Cardiac condition including congestive heart failure or arrhythmia, uncontrolled diabetes mellitus, significant respiratory disease or known immunosuppression which required hospitalization within the previous 6 months

14. Baseline serum creatinine level > 1.8 mg/dl

15. Known upper tract renal disease

16. Cystolithiasis or chronic hematuria within 3 months prior to study treatment

17. Active prostatitis

18. Previous rectal surgery other than hemorrhoidectomy, or history of rectal disease

19. History of pelvic irradiation or radical pelvic surgery

20. Patient is interested in future fertility

21. Coagulation disturbances not normalized by medical treatment

22. Acute urinary retention requiring an indwelling catheter

23. Known major iliac arterial occlusive disease

24. Allergy to iodinated contrast agents

25. Hypersensitivity to gelatin products

4 Study Design

This is a phase 3 multicenter, prospective study designed to evaluate the safety and effectiveness of treating patients with symptomatic BPH with PAE using Embosphere Microspheres compared to conventional TURP. Approximately 186 patients with LUTS due to BPH will be enrolled using a 2:1 ratio, with approximately 124 receiving treatment with PAE and 62 receiving conventional TURP, in order to have 100 patients in the PAE and 50 patients in the TURP arm complete 12 month follow up.

The study will consist of a screening period in which patient eligibility will be determined and baseline assessments performed. Once eligibility is confirmed, patients will be enrolled within 4 weeks of baseline imaging to receive either TURP or PAE with Embosphere Microspheres. After treatment, patients will return for follow-up visits at Months 1, 3, 6, and 12. At each of these visits patients will complete IPSS and IIEF questionnaires and have a physical exam, laboratory assessments (including PSA), a DRE, and a transrectal ultrasound of the prostate. At each visit patients will have a cystoscopy and proctoscopy if medically indicated. Cystoscopy is necessary in all cases of hematuria (injury associated with bleeding). Proctoscopy is necessary in all cases of bleeding per the rectum. An MRI of the prostate will be conducted at the 3 and 12 month visits. Uroflowmetry testing will be performed at the 1 and 12 month visits, and at other visits if medically indicated. MRIs will be assessed by blinded Central Reviewers.

The primary endpoint will be improvement of symptoms from BPH evaluated using the IPSS at 12 months post treatment. Patients will continue to be followed annually for up to 4 additional years. At a minimum, patients will be requested to complete the IPSS and IIEF questionnaires by telephone, email or mail once per year during this long term follow up period. Patients who are willing to return to the clinic will have a physical exam, MRI of the prostate, digital rectal exam (DRE), transrectal ultrasound of the prostate, PSA, and uroflowmetry testing performed each year. Treatments for LUTS due to BPH after the study treatment and 12 month follow up are complete will be documented during the long term follow up period to the extent possible. This long term follow up data will be summarized and submitted separately from the data for the initial 12 months of this study.

Safety will be evaluated throughout the initial 12 months of the study by assessing adverse events, as well as changes in laboratory values, and findings on physical examination. Concomitant medication usage will be assessed. A follow up ECG will be performed at the 12 month visit.

Patient recruitment is anticipated to take approximately 2 years. Duration of each patient's participation is expected to be 5 years, including a 4 year long term follow up period. The total duration of the study will be approximately 7 years, including long term follow up.

5 Enrollment and Blinding

Patients will be recruited separately to receive either PAE with Embosphere Microspheres or conventional TURP on a 2:1 basis, with more patients enrolled in the PAE group. Enrollment will occur after informed consent has been signed and it has been confirmed that the patient meets all study eligibility criteria.

Patients will be recruited at each site in blocks of 15. The first 10 patients meeting all the inclusion criteria and none of the exclusion criteria will be enrolled in the PAE cohort. The next 5 patients meeting all the inclusion criteria and none of the exclusion criteria will be enrolled in the TURP cohort. Patients will not be able to choose their treatment arm, only to accept or decline participation in the study cohort that is being enrolled. Patients in the TURP cohort will be offered a stipend of $75.00 per completed study visit in consideration of the additional visits and evaluations they will undergo as part of the study, and which would not be standard of care if they were treated by TURP outside the study.

It is not possible to blind either the patient or the treating physician to treatment group because the two treatment methods are easily identifiable. Evaluation of size and location of prostate by MRI will be assessed by Central Reviewers who will not be given any treatment information. Patient MRIs will be identified by study ID number only.

6 Treatment and Assessment

After patients have been treated, follow up visits will take place at 1, 3, 6, and 12 months, $\pm$ 2 weeks for each visit, calculated from the day of treatment (Day 1) according to the Schedule of Events (Appendix A) and Study Flow Chart (Appendix B). Long term surveillance data for up to 4 additional years will be collected.

Patients who receive PAE with Embosphere Microspheres procedure will be treated with a single procedure. The microspheres will be mixed with a contrast agent and will be delivered to the arteries supplying the prostate via microcatheter. The occlusion endpoint will be stasis.

Patients who receive conventional TURP will be treated with a single procedure according to the standard of care for their institution.

6.1 Visit -1: Screening/Baseline (within 4 weeks of enrollment unless stated otherwise)

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

- Obtain Informed Consent
- Medical history, including demographics
- Concurrent medical conditions
- Physical exam, including vital signs, height (baseline only), weight, and genitourinary evaluation
- Baseline serum blood tests
    - Complete Blood Count (CBC) including red blood count (RBC), white blood count (WBC), platelets, hemoglobin, hematocrit, neutrophils
    - Chemistry including albumin, alkaline phosphatase, blood urea nitrogen (BUN), serum creatinine, total bilirubin, prothrombin time (PT)
- Urinalysis
    - Specific gravity, protein, glucose, blood, leukocytes, nitrites
- Prostate Specific Antigen (PSA) and free PSA
- Digital rectal exam (DRE)
- Transrectal ultrasound of the prostate
- MRI of the prostate
- Urodynamic testing including maximum flow rate (Qmax), average flow rate, detrusor muscle pressure (Pdet), voided volume (minimum voided volume must be >125 mL for a valid test), total time of voiding, and post void residual volume (PVR) within 3 months prior to enrollment
- International Prostate Symptom Score (IPSS)
- International Index of Erectile Function (IIEF)
- Electrocardiogram (ECG)
- Cystoscopy within 3 months prior to enrollment
    - Examination will include evaluation for bladder neck obstruction or contracture, urethral strictures, sphincter abnormalities, bladder cancer, or other disorders of the bladder, urethra or prostatic urethra and assessment of prostate size, lobar distribution and anatomy and length from the verumontanum to the bladder neck
- Recording of concomitant medications
- The following patients must have undergone prostate biopsy with a minimum of 12 cores and have had a negative histopathology report within the prior 12 months to be enrolled in the study:
    - Patients with DRE findings suspicious for prostate cancer
    - Patients with baseline PSA levels > 10 ng/mL
    - Patients with baseline PSA levels >2.5 ng/mL and $\leq$ 10ng/mL AND free PSA < 25% of total PSA

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

6.2 Visit 1: Study Treatment

Patients will be enrolled within 4 weeks of baseline imaging.

PAE with Embosphere Microspheres will be done following the procedure in Appendix C. Conventional TURP will be done following the institution's standard of care.

Treatment data recorded will include the following:

- Date of procedure
- Date and time of hospital admission and discharge
- Medications received immediately prior to and during the procedure
- Date and time of urinary catheter insertion and removal (if patient is discharged with catheter in place, catheter removal information will be collected at the first follow up visit)
- Medications at time of discharge
- Adverse events

6.3 Visit 2: Month 1 (4 weeks ± 2 weeks from Visit 1)

Patients will have the following assessments performed:

- Physical exam including vital signs, weight, and genitourinary evaluation
- Blood and urine laboratory evaluations, including the same parameters as at baseline
- Prostate Specific Antigen (PSA) and free PSA
- Digital rectal exam (DRE)
- Transrectal ultrasound of the prostate
- Uroflowmetry testing, including the same parameters as at baseline except Pdet
- International Prostate Symptom Score (IPSS)
- International Index of Erectile Function (IIEF)
- Cystoscopy, if medically indicated, and necessary in all cases of hematuria.
- Proctoscopy, if medically indicated, and necessary in all cases of bleeding per the rectum.
- Adverse Events
    - Including clinically significant changes in laboratory values from baseline
- Concomitant Medications

Effort must be made to have patients complete the physical assessments of this visit. If patient refuses to come in for a visit, at a minimum the patient should complete the IPSS and IIEF questionnaires and report any adverse events by telephone.

6.4 Visit 3: Month 3 (12 weeks ± 2 weeks from Visit 1)

Patients will have the following assessments performed:

- Physical exam including vital signs, weight, and genitourinary evaluation
- Blood and urine laboratory evaluations, including the same parameters as at baseline
- Prostate Specific Antigen (PSA) and free PSA
- Digital Rectal Exam (DRE)
- Transrectal ultrasound of the prostate
- MRI of the prostate
- International Prostate Symptom Score (IPSS)
- International Index of Erectile Function (IIEF)
- Adverse Events
    - Including clinically significant changes in laboratory values from baseline
- Concomitant Medications
- Cystoscopy and/or urodynamic or uroflowmetry testing if medically indicated. Cystoscopy will be necessary in all cases of hematuria.

Effort must be made to have patients complete the physical assessments of this visit. If patient refuses to come in for a visit, at a minimum the patient should complete the IPSS and IIEF questionnaires and report any adverse events by telephone.

6.5 Visit 4: Month 6 (24 weeks ± 2 weeks from Visit 1)

Patients will have the following assessments performed:

- Physical exam including vital signs, weight, and genitourinary evaluation
- Blood and urine laboratory evaluations, including the same parameters as at baseline
- Prostate Specific Antigen (PSA) and free PSA
- Digital rectal exam (DRE)
- Transrectal ultrasound of the prostate
- International Prostate Symptom Score (IPSS)
- International Index of Erectile Function (IIEF)
- Adverse Events
    - Including clinically significant changes in laboratory values from baseline
- Concomitant Medications
- Cystoscopy and/or urodynamic or uroflowmetry testing if medically indicated. Cystoscopy will be necessary in all cases of hematuria.

Effort must be made to have patients complete the physical assessments of this visit. If patient refuses to come in for a visit, at a minimum the patient should complete the IPSS and IIEF questionnaires and report any adverse events by telephone.

6.6 Visit 5: Month 12 (52 weeks ± 2 weeks from Visit 1)

Patients will have the following assessments performed:

- Physical Exam, including vital signs, weight, and genitourinary evaluation
- Blood and urine laboratory evaluations, including the same parameters as at baseline
- Prostate Specific Antigen (PSA) and free PSA
- Digital rectal exam (DRE)
- Transrectal ultrasound of the prostate
- MRI of the prostate
- Uroflowmetry testing including the same parameters as at baseline, except Pdet
- International Prostate Symptom Score (IPSS)
- International Index of Erectile Function (IIEF)
- Electrocardiogram (ECG)
- Adverse Events
    - Including clinically significant changes in laboratory values from baseline
- Concomitant Medications
- Cystoscopy, if medically indicated, and necessary in all cases of hematuria.

Effort must be made to have patients complete the physical assessments of this visit. If patient refuses to come in for a visit, at a minimum the patient should complete the IPSS and IIEF questionnaires and report any adverse events by telephone.

6.7 Annual Long Term Follow-up

Patients will be followed for up to 4 additional years after the 12 month visit (Visit 5). Patients will be encouraged to come to the clinic on an annual basis for the following evaluations:

- Physical Exam, including vital signs, weight, and genitourinary evaluation
- Prostate Specific Antigen (PSA) and free PSA
- Digital rectal exam (DRE)
- Transrectal ultrasound of the prostate
- MRI of the prostate
- Uroflowmetry testing including the same parameters as at baseline, except Pdet
- International Prostate Symptom Score (IPSS)
- International Index of Erectile Function (IIEF)
- Documentation of any new treatments for BPH and/or LUTS

Patients who are unwilling to come to the clinic will be asked to complete the IPSS and IIEF questionnaires and provide information of any new treatments for BPH and/or LUTS by telephone, email or mail. Information on medications and adverse events will not be captured during the long term follow up period following the 12 month visit.

7 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 patients from the study for any of the following reasons:

- Adverse events
- Refusal of treatment
- Patient request
- Inability to complete study procedures
- Lost to follow up
- Non compliance with study requirements

If a patient is withdrawn or discontinued from the study, the reason for withdrawal from the study will be recorded in the source documents and on the Study Termination CRF. All patients withdrawn from the study will be encouraged to complete, if possible, all clinical evaluations scheduled for the 12 month visit. All adverse events should be followed as described in Section 8. Patients who are withdrawn from the study for any reason will not be replaced.

The study may be terminated by the Sponsor at any time.

8 Adverse Events

8.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject and does not necessarily have to 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 medicinal product 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 an SAE as defined below.

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

Patients should 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 should be recorded on the appropriate AE CRF. In order to capture the most potentially relevant safety information during this study, it is important that the Investigators record AE terms accurately and consistently throughout the study. Wherever possible, a specific disease or syndrome should be reported on the CRF rather than the associated individual 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 CRF.

All adverse events will be assessed for severity, relationship to study treatment, subsequent treatment required for the adverse event, and outcome/resolution. This information will be recorded on the Adverse Event CRF pages.

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

- For cystoscopy, PAE and TURP:
  - Burning in the urethra, urinary infection, hematuria, pain
- For PAE and TURP:
  - Hematospermia, hemorrhage, injury to bladder, including bladder neck, ureteral orifice or trigone, impact on future fertility
- For TURP:
  - Ejaculatory dysfunction, incontinence, erectile dysfunction
- For PAE:
  - Vasospasm, rectorrhagia, inguinal hematoma, bladder/bladder neck ischemia and necrosis, bladder resection, allergic reaction to microspheres or contrast agent, radiation exposure, vascular perforation.

Serious Adverse Event (SAE)

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

- **Results in death.**

- **Is life-threatening**, where life-threatening means that the subject was at immediate risk of death from the reaction 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 in-patient hospitalization or prolongation of existing hospitalization**. Hospitalization 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 subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- **Results in persistent or significant disability/incapacity,** where disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- **Is a congenital anomaly/birth defect.**
- **Is an important medical event as defined 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 or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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 they are not interchangeable. 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 subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. 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 a SAE, unless the patient would be admitted to the hospital or the event would meet any other of the 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 above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

  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 defined above. Complications associated with surgical procedures or study treatments resulting in one of the outcomes above are considered SAEs.

8.2 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. Adverse events will be evaluated for severity using NCI CTCAE (Common Toxicity Criteria for Adverse Events) where applicable.

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

Serious adverse events (SAEs) must be reported to Merit Medical or its representative within 24 hours of knowledge of their first occurrence. SAEs that occur following the signature of the informed consent but prior to treatment will not be reported.

8.3 Serious Adverse Event Reporting

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, must be reported to the Sponsor immediately (not to exceed 24 hours within site notification of the event) using the electronic SAE form provided by the Sponsor. The SAE must be completely described on the AE CRF as well as the provided safety report form.

Safety Contact Information:	Melodie R Domurad PhD Email: mdomurad@merit.com Phone: +781 681 7912

9 Symptom Assessments

9.1 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 questionnaire can be found in Appendix D.

9.2 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.

10 Statistical Analysis

10.1 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 from all investigational sites will be pooled in the analyses. Summary tables will present data for both treatment groups and overall, where appropriate. 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 procedure.

Unscheduled data, such as information from unscheduled visits, repeat laboratory tests, or Investigator comments, will be included in the data listings. In general, these data will be excluded from the summary tables unless otherwise specified.

Any outliers detected during the review of the data will be investigated. If needed 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 SAS® (Statistical Analysis System), version 9.1 or higher.

10.2 Sample Size Calculations

Assuming 95% of patients in both groups improve by at least 3 points on the IPSS total score from baseline to 12 months, with 150 patients enrolled in a 2:1 ratio in favor of PAE with Embosphere Microspheres (ie, 100 treated with PAE and 50 treated with TURP), the lower limit

of the 1 sided-95% confidence interval for the difference in proportions for the two treatments (PAE-TURP) will be expected to exceed -10% with 88% power.

It is anticipated that 20% of patients will not complete the 12 month IPSS assessment; therefore a total of 186 patients will be enrolled at 12 sites in order to have 100 patients in the PAE group and 50 patients in the TURP group with 12 month IPSS data.

10.3 Analysis Populations

10.3.1 Safety Population (SAF)

All patients who have a PAE with Embosphere Microspheres or TURP will be included in the Safety Population.

10.3.2 Intent-to-Treat Population (ITT)

The Intent- to-Treat (ITT) Population is defined as all patients enrolled in the study, regardless of treatment status. This will be the primary population for the efficacy analyses.

10.3.3 Evaluable Population (EVAL)

All patients who have a PAE with Embosphere Microspheres or TURP and who have valid IPSS data for the 12 month time point and who do not have any major protocol violations will be included in the Evaluable Population.

10.4 Demographic and Baseline Characteristics

Patient characteristics will include the following:

- Patient demographics (age, gender; race, ethnicity, if possible)
  - Note: *Many EU countries do not allow collection of information about race or ethnicity*.
- Baseline BPH/LUTS characteristics (size of prostate by MRI, PSA, free PSA, maximum flow rate (Qmax), average flow rate, detrusor muscle pressure (Pdet), voided volume, total time of voiding, and post void residual volume (PVR))
- Clinically significant medical history
- Concurrent medical conditions
- Prior BPH/LUTS therapy
- Concomitant medications and treatments (these will be recorded throughout the study)

10.5 Efficacy Analysis

10.5.1 International Prostate Symptom Score (IPSS)

The primary efficacy outcome will be based on the IPSS. The IPSS is a frequently used, validated 8 item (7 symptom questions and 1 quality of life question) instrument which can be performed multiple times 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 seven symptoms in the past month: incomplete emptying, frequency, intermittency, urgency, weak 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 seven symptoms. The eighth item is an assessment of patient quality of life (QOL) due to urinary symptoms and does not contribute to the IPSS total score calculation.

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

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

The proportion of patients improving at least 3 points on the IPSS total score at the 1 month, 3month, 6 month and 12 month time points will be summarized for both treatment groups and the corresponding 95% confidence intervals will be calculated.

The primary efficacy analysis is the comparison of the proportion of patients in both treatment groups who have improved by at least three points on the IPSS total score from baseline to 12 months for the ITT analysis population. The 95% one-sided confidence interval will be calculated for the difference in proportions between the two treatment groups (PAE-TURP). Non-inferiority will be declared if the lower limit of the confidence interval is -10% or higher (ie, the difference is no more than 10%).

A secondary analysis of the proportion of patients in both treatment groups who have improved by at least one IPSS symptom category (ie, severe to moderate, severe to mild, severe to moderate) from baseline to 12 months will be performed. The 95% one-sided confidence interval will be calculated for the difference in proportions between the two treatment groups (PAE-TURP).

Secondary analyses of the total IPSS score analyzed as a continuous outcome will be performed. The total IPSS score will summarized for both treatment groups for the baseline, 1 month, 3 month, 6 month, and 12 month timepoints, including change from baseline. The difference in treatment means will be calculated for each timepoint, including the corresponding 95% confidence interval.

The single IPSS QOL item will be summarized separately.

Similar IPSS analyses will also be performed for the Evaluable population.

10.5.2 Duration of hospitalization

The duration of hospitalization associated with the procedure will be calculated in hours. This will be a key secondary analysis in support of the indication for use and performance of PAE. Summary statistics will be calculated for both groups. The difference in treatment means will be calculated, including the corresponding 95% confidence interval, and treatment groups will be compared using Student's t-test for the ITT and Evaluable populations. If the distribution of the data is found to differ substantially from normal, appropriate methods will be used to analyze the data, including a data transformation or time to event analysis. It is expected that the PAE group will have a statistically significant improvement in duration of hospitalization compared to the TURP group.

10.5.3 Duration of post procedure catheterization

The duration of post procedure catheterization will be calculated in hours. Summary statistics will be calculated for both groups. This will be a key secondary analysis in support of the indication for use and performance of PAE. The difference in treatment means will be calculated, including the corresponding 95% confidence interval and treatment groups will be compared using Student's t-test for the ITT and Evaluable populations. If the distribution of the data is found to differ substantially from normal, appropriate methods will be used to analyze the data, including a data transformation or time to event analysis. It is expected that the PAE group will have a statistically significant improvement in duration of post-procedure catheterization compared to the TURP group.

10.5.4 Peak urine flow rate (Qmax)

The peak urine flow rate (Qmax) from the urodynamic and uroflowmetry assessments will be summarized for both treatment groups for the baseline and 12 month timepoints, including change from baseline. The difference in treatment means will be calculated for each timepoint, including the corresponding 95% confidence interval for the ITT and Evaluable populations.

10.5.5 Post void residual urine volume (PVR)

The post void residual volume (PVR) from the urodynamic and uroflowmetry assessments will be summarized for both treatment groups for the baseline and 12 month timepoints, including change from baseline. The difference in treatment means will be calculated for each timepoint, including the corresponding 95% confidence interval for the ITT and Evaluable populations.

10.5.6 Detrusor muscle pressure (Pdet)

The Detrusor muscle pressure (Pdet) from the urodynamic assessments at baseline will be summarized for both treatment groups.

10.5.7 International Index of Erectile Function (IIEF)

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

- Erectile Function (items 1, 2, 3, 4, 5, 15)
- Orgasmic Function (items 9, 10)
- Sexual Desire (items 11, 12)
- Intercourse Satisfaction (items 6, 7, 8)
- Overall Satisfaction (items 13, 14)

Each subscale will be summarized separately for both treatment groups for the baseline, 1 month, 3 month, 6 month, and 12 month timepoints, including change from baseline. The difference in treatment means will be calculated for each timepoint, including the corresponding 95% confidence interval for the ITT and Evaluable populations.

10.5.8 Mean prostate volume

The mean prostate volume as assessed by MRI will be summarized for both treatment groups for the baseline, 3 month and 12 month timepoints, including change from baseline. The difference in treatment means will be calculated for each timepoint, including the corresponding 95% confidence interval for the ITT and Evaluable populations.

10.5.9 Prostate specific antigen (PSA)

Prostate specific antigen (PSA) will be summarized for both treatment groups for the baseline, 1 month, 3 month, 6 month, and 12 month timepoints, including change from baseline. The difference in treatment means will be calculated for each timepoint, including the corresponding 95% confidence interval for the ITT and Evaluable populations.

10.5.10 Additional Variables from Urodynamic and Uroflowmetry Testing

The average flow rate, voided urine volume and total time of voiding from the urodynamic and uroflowmetry assessments will be summarized for the baseline and 12 month timepoints, including change from baseline.

10.5.11 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 prior to unblinding the data 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.

Multiple imputation (MI) methods will be used to assign values to those patients in the ITT population with missing data for the primary effectiveness analysis. This approach assumes the data is missing at random (MAR). MI introduces appropriate random error into the imputation process making it possible to obtain approximately unbiased estimates of all parameters. An appropriate MI model that incorporates random variation which will be run 3-5 times to generate several imputed "complete" datasets which will allow for good estimates of the standard errors.

In order to assess the robustness of the statistical inferences based on the primary imputation method (MI) for the primary effectiveness analysis, sensitivity analyses will be performed including but not limited to a "worst-case imputation," and a "tipping point analysis."

10.5.12 Adjustment for Multiplicity

In addition to the primary analysis based on the IPSS total score, key secondary analyses will be performed comparing the treatment groups on the Duration of Post-Procedure Catheterization and Duration of Hospitalization post procedure for the ITT population. These analyses will be used to support the indication for use and performance of PAE in the treatment of BPH. The Bonferonni Correction will be used to adjust these secondary analyses in order to control the experimentwise (overall) Type I error rate at the 0.05 level. No adjustment will be performed on the primary efficacy outcome analysis.

Multiple inferences for key secondary outcomes will be conducted only if the primary effectiveness outcome is met.

10.6 Safety Analysis

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

10.6.1 Adverse Events

Safety summaries will include the incidence of treatment-emergent adverse events (TEAEs). Treatment-emergent adverse events (TEAEs) are defined as any event 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 adverse events. Adverse events recorded on the CRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

All TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summaries will present data for both treatment groups by System Organ Class (SOC) and Preferred Term. TEAEs will be evaluated for severity using the CTCAE when available.

A summary of the total number of reported TEAEs will be generated for both treatment groups. In addition, TEAEs will be summarized based on the number of patients experiencing an event, not the number of AEs experienced. For example, if a patient reports the same AE on 3 separate occasions that patient will be counted only once for that preferred term. Patients reporting more than one AE in a SOC will be counted only once in the SOC total. The denominator used for calculation of the percentages will be the number of patients in the Safety population in each treatment group.

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

- Overall TEAEs
- Severe TEAEs (grade 3 or higher)
- TEAEs related to treatment
- Serious adverse events (SAEs)
- Serious adverse events related to treatment
- TEAEs resulting in death

Treatment groups will be compared on adverse event rates using Fisher's Exact Test.

10.6.2 Laboratory Evaluations

Summary statistics for baseline and change from baseline will be summarized for both treatment groups for all hematology and chemistry parameters for the 1, 3, 6 and 12 month timepoints. Urinalysis data will be presented in the data listings only.

10.6.3 Vital Signs

Summary statistics for baseline and change from baseline will be summarized for the 1, 3, 6 and 12 month timepoints for both treatment groups for the following vital sign parameters:

- Blood pressure (mmHg)
- Weight
- Pulse (beats per minute)
- Respiration rate (breaths per minute)
- Temperature (^{o}C)

10.6.4 Physical Examinations

Data from physical exams (scheduled and unscheduled) will be presented in the data listings. All pre-treatment clinically significant findings, as determined 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.

10.6.5 Electrocardiogram (ECG)

Data from the baseline and 12 month ECGs will be presented in the data listings. All pre-treatment clinically significant findings, as determined by the Investigator, will be reported as concurrent medical conditions. All clinically significant findings on the 12 month ECG will be reported as adverse events.

10.6.6 Cystoscopy

Cystoscopy results will be summarized by treatment group for baseline visits. Any clinically significant findings on the post-baseline cystoscopies will be reported as adverse events.

10.6.7 Proctoscopy

Any clinically significant findings on proctoscopies will be reported as adverse events.

10.6.8 Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be presented by Drug Class and preferred term. Patients taking a medication multiple times during the study will be counted once for the Drug Class and preferred term in the summary tables. Concomitant medications will be summarized by treatment group.

11 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be formed consisting of at least 3 individuals with expertise and experience in clinical trials and safety evaluations, but without direct involvement in the conduct of the study. The exact responsibilities, procedures, and guidelines used to manage the DSMB are described in a separate charter.

12 Records and Confidentiality

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

13 Quality Control and Assurance

This study will be initiated and conducted under the sponsorship of Merit Medical Systems, Inc. through its wholly owned subsidiary BioSphere Medical. The sponsor will supply electronic CRFs to all sites. Representatives of BioSphere Medical will monitor the study to verify study data, medical records, and CRF data in accordance with current ICH, GCPs and other applicable regulations and guidelines.

14 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) E6 for Good Clinical Practice (GCP): Consolidated Guidance and the appropriate regulatory requirement(s). The Investigators 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 should be established at the beginning of the study, maintained for the duration of the trial and retained according to the appropriate regulations.

15 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where the IRB/EC approval has been obtained. The protocol, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the Investigator.

16 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the patient prior to any study specific procedures being performed. The informed consent form used at each site will be approved by the IRB/EC 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 applicable regulatory requirement(s).

17 Patient Confidentiality

In order to maintain patient privacy, all CRFs, study reports and communications will identify the patient the assigned patient ID number only. The Investigator will grant monitor(s) and auditor(s) from BioSphere Medical, or its designee, and regulatory authority(ies) access to the patients' original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

18 Protocol Compliance

The Investigators will conduct the trial in compliance with the protocol provided by BioSphere Medical, and given approval/favorable opinion by the IRB/EC and the appropriate regulatory authority(ies), if required. Modifications to the protocol should not be made without agreement of the Investigator and BioSphere Medical. Changes to the protocol potentially affecting safety or efficacy will require written IRB/EC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/EC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/EC. BioSphere Medical will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

A record of patients screened, but not entered into the study, will be maintained.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to the patient, the Investigator will contact BioSphere Medical or designee, if circumstances permit, to discuss the planned course of action and the action will be fully documented in the case report form and source documentation.

19 Monitoring, Verification of Data, Audit and Inspection

A BioSphere Medical monitor, or designee, will visit each center periodically to monitor the progress of the clinical trial and review CRFs and original source documents with the study personnel, to verify accuracy of data recording. Periodically some/all of the facilities used in the trial (e.g., laboratory) may be reviewed or inspected by the IRB/EC and/or regulatory authorities.

The Investigator will ensure that the trial participants are aware of and consent that personal information may be reviewed during the data verification process as part of the monitoring/auditing by properly authorized agents of BioSphere Medical or subject to inspection by regulatory authorities. The audit or inspection may include, for example, a review of all source documents, drug records, original clinical medical notes, some or all of the facilities used in the trial. During monitoring or audit/inspection, participation and personal information is treated as strictly confidential to the extent the applicable law permits and is not made publicly available

20 Data Recording and Retention of Study Data

In compliance with Good Clinical Practice (GCP), the medical records/medical notes, etc. should be clearly marked and permit easy identification of participation by an individual in the specified clinical trial. The Investigator must record all data with respect to protocol procedures, drug administration, laboratory data, safety data and efficacy ratings on the BioSphere Medical CRFs.

If the Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention, BioSphere Medical must be notified (in writing) so that adequate provision can be made with regard to the trial documents.

Trial documents must be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region by BioSphere Medical. Documents must be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with BioSphere Medical, who will inform the Investigator, in writing, as to when these documents no longer need to be retained.

21 Confidentiality, Publication and Disclosure Policy

The Investigators understand that BioSphere Medical will use the information developed in the clinical study in connection with the development of the study treatment. This information may be disclosed to other study Investigators, the FDA, and other government agencies. All information disclosed to the Investigators by BioSphere Medical for the purpose of having the Investigators conduct the clinical trial described in this protocol or generated by the Investigators as results in the clinical trial shall be treated by the Investigators as strictly confidential. The Investigators shall not use such information other than for the purpose of conducting the clinical trial and may not disclose such information to others, except when such disclosure is to colleagues and/or employees who reasonably require the information to assist in carrying out the clinical trial and who are bound by like obligations of confidentiality. Notwithstanding, the Investigators may use or disclose to others any information which: (i) was known to the Investigators prior to the date of its disclosure, (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the Investigators on a nonconfidential basis by a third party who is not obligated to BioSphere Medical or any other party to retain such information in confidence.

Biosphere Medical acknowledges that the Investigators have certain professional responsibilities to report to the scientific community on findings in clinical investigations they conduct. The Investigators shall have the right to publish the results of research performed under this protocol, provided such publication does not disclose any confidential information or trade secrets of BioSphere Medical (other than the data). The study is a multi-center protocol, and as such the Investigators agree not to independently publish their findings except as part of an overall multi-center publication, unless specifically approved in writing by BioSphere Medical.

22 Bibliography

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APPENDIX A: Schedule of Study Events

	Visit -1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Annual Long Term Follow-Up Visits
	Baseline (within 4 wks. of enrollment)	Study Treatment (Day 1)	Month 1 (4 wks ± 2 wks of Visit 1)	Month 3 (12 wks ±2 wks of Visit 1)	Month 6 (24 wks ±2 wks of Visit 1)	Month 12 (52 wks ± 2 wks of Visit 1)	Annually for up to 4 years following 12 month visit
Informed Consent	X						
Eligibility criteria assessment	X						
Demographics	X						
Medical History and Concurrent Medical Conditions	X						
Prostate Biopsy[1]	X						
Physical Examination, including weight and genitourinary exam	X		X	X	X	X	X
Vital signs	X		X	X	X	X	
Hematology (CBC) / Serum Chemistry	X		X	X	X	X	
Urinalysis	X		X	X	X	X	
Prostate Specific Antigen (PSA)	X		X	X	X	X	X
Digital Rectal Exam (DRE)	X		X	X	X	X	X
Transrectal Ultrasound	X		X	X	X	X	X
MRI of the Prostate	X			X		X	X
IPSS	X		X	X	X	X	X
IIEF	X		X	X	X	X	X
Electrocardiogram (ECG)	X					X	
Urodynamic/UroflowmetryTesting[2]	X		X	X (if medically indicated)	X (if medically indicated)	X	X
Cystoscopy[3]	X		X (if medically indicated)	X (if medically indicated)	X (if medically indicated)	X (if medically indicated)	
Proctoscopy[3]			X (if medically indicated)				
Enrollment [4]		X					
Study Treatment[5]		X					
Post treatment evaluation[6]		X					
Adverse Events		X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	
Protocol Violations	X	X	X	X	X	X	X
Documentation of treatments for BPH and/or LUTS							X

[1] Prostate biopsy with minimum of 12 cores required within the prior 12 months for patients with DRE findings suspicious for prostate cancer, baseline PSA levels > 10 ng/mL, or baseline PSA levels >2.5 ng/mL and ≤ 10ng/mL AND free PSA < 25% of total

[2] Urodynamic testing including maximum flow rate (Qmax), average flow rate, detrusor muscle pressure (Pdet), voided volume (minimum voided volume must be >125 mL for a valid test), total time of voiding, and post void residual volume (PVR); baseline urodynamic testing must be performed within 3 months prior to enrollment; after screening Uroflowmetry will include the same parameters as Urodynamics except Pdet

[3] Cystoscopic examination will include evaluation for bladder neck obstruction or contracture, urethral strictures, sphincter abnormalities, bladder cancer, or other disorders of the bladder, urethra or prostatic urethra and assessment of prostate size, lobal distribution and anatomy and length from the

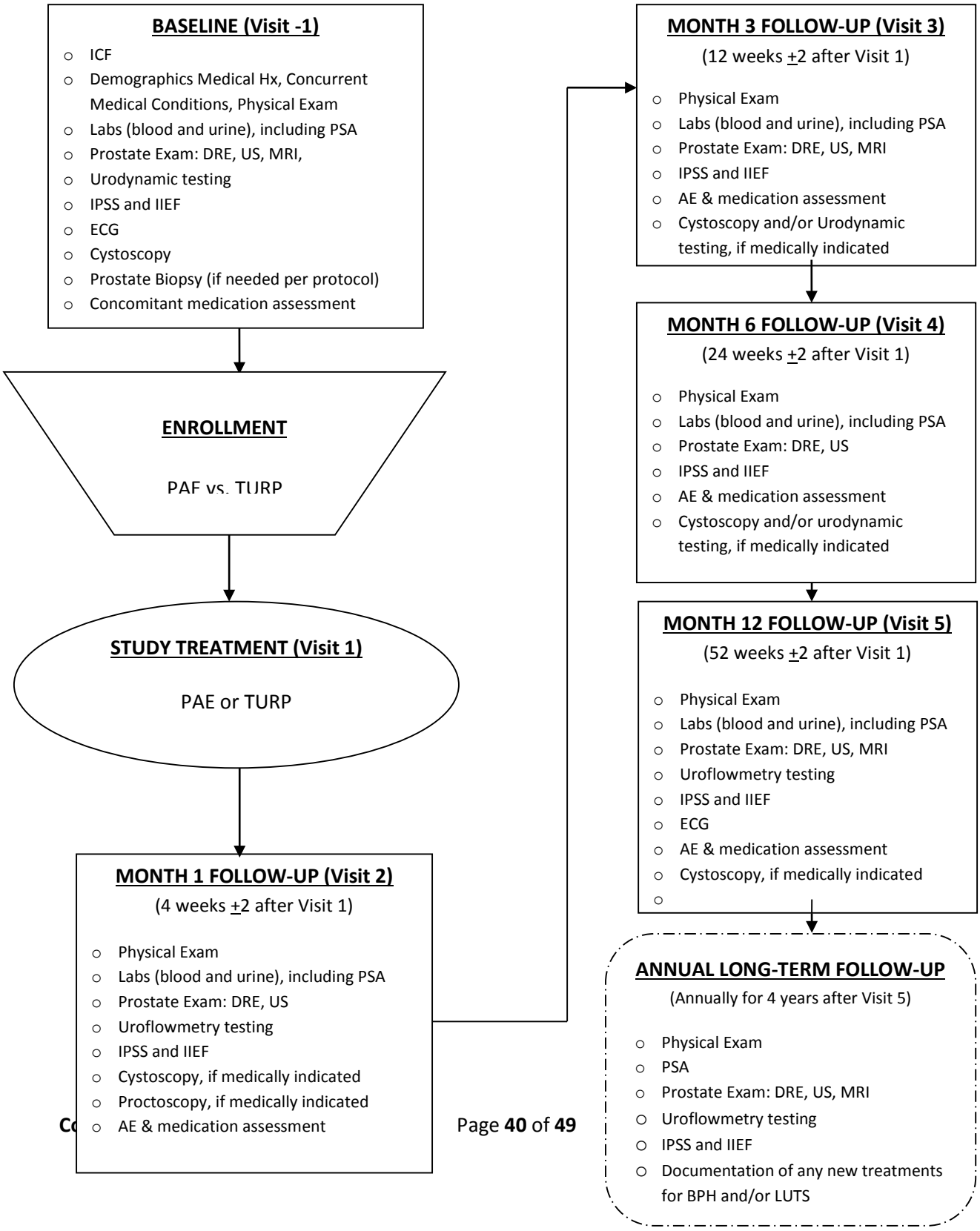
verumontanum to the bladder neck; baseline cystoscopy must be performed within 3 months prior to enrollment. Cystoscopy will be necessary in all cases of hematuria. Proctoscopy will be necessary in all cases of bleeding per the rectum.

[4] Patients will be enrolled within 4 weeks of baseline MRI imaging

[5] Patients will be treated with PAE using Embosphere Microspheres or conventional TURP based on cohort enrollment

[6] Post treatment evaluations includes: duration of hospital stay, procedural medications and post treatment catheter duration

APPENDIX B: Study Flow Chart



APPENDIX C

APPENDIX D

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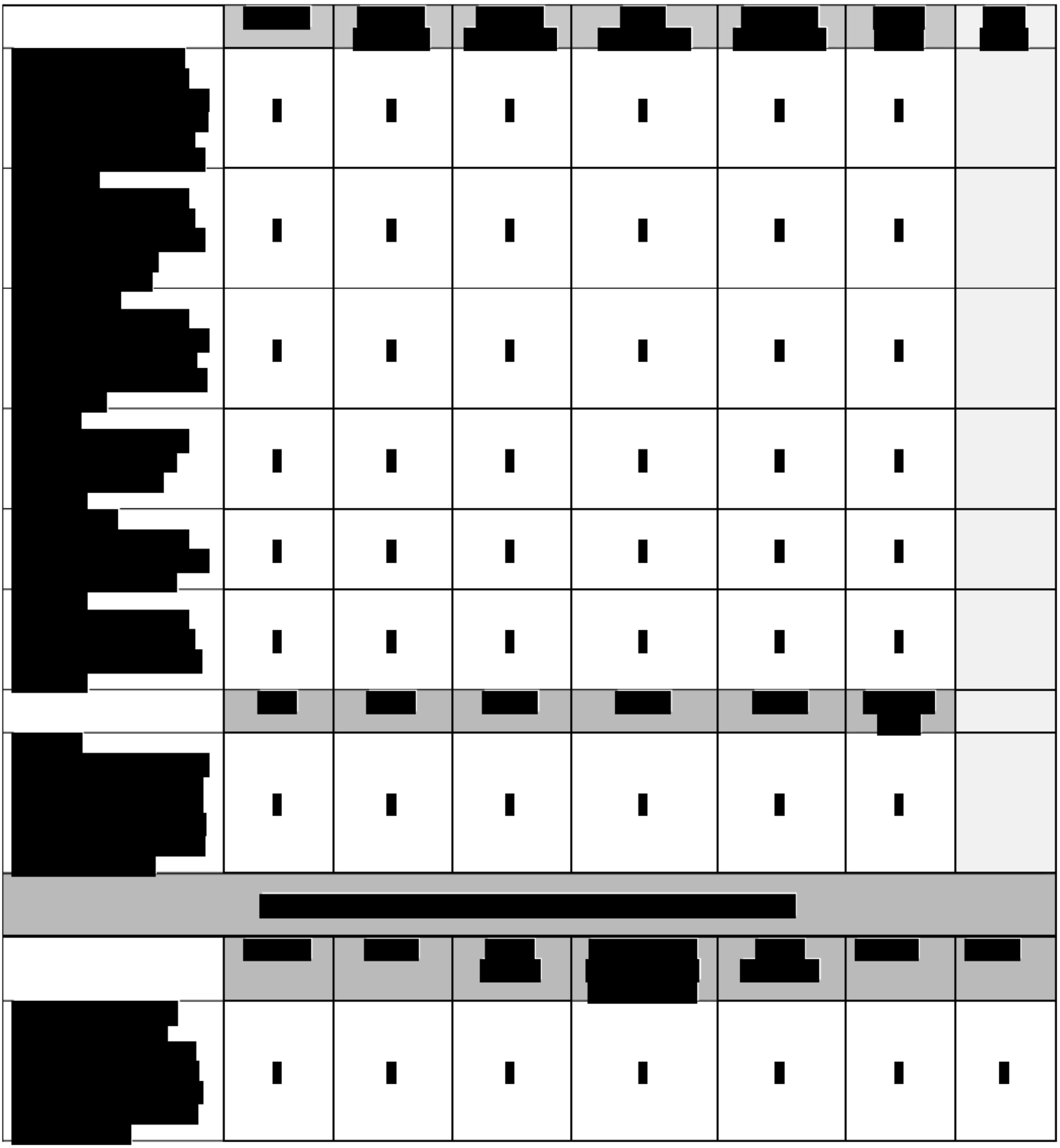
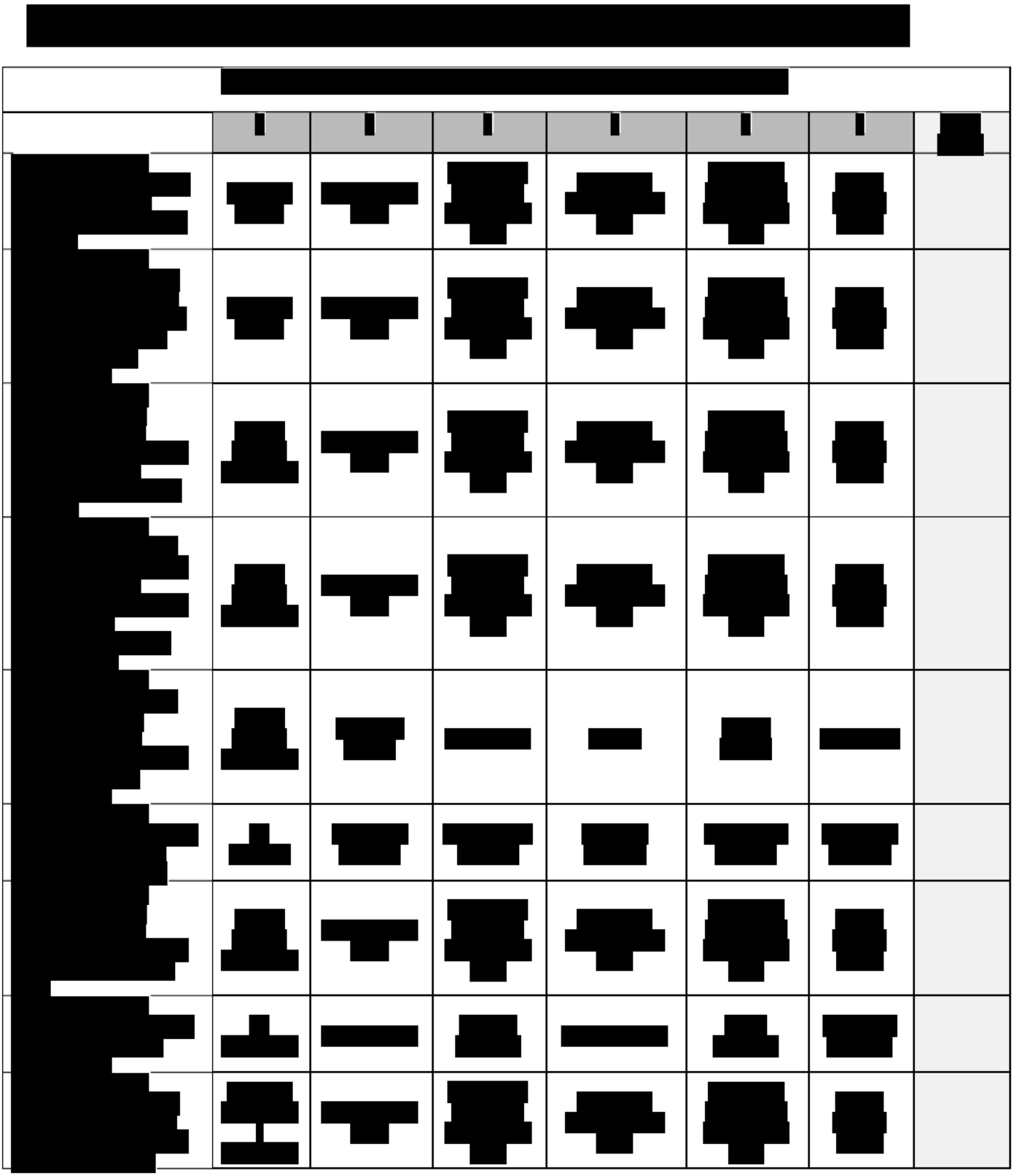


APPENDIX E



APPENDIX F

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