**NCT02930889**

# Title: Prostate Artery Embolization (PAE) for Lower Urinary Tracts Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH)

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Jafar Golzarian M.D.
Professor and Head, Interventional Radiology
University of Minnesota
Department of Radiology
golzarian@umn.edu

## GENERAL INFORMATION

### Name and address of the person authorized to sign the protocol and amendments

Jafar Golzarian, MD
MMC 292
420 Delaware St. SE
Minneapolis MN 55455
golzarian@umn.edu
612-626-5388

### Name and address of study monitor

Vu Huyhn
717 Delaware St
2nd Floor
Minneapolis MN 55455
huyn0089@umn.edu

### Name, title, address and telephone number(s) of the medical expert for the trial

Jafar Golzarian, MD
MMC 292
420 Delaware St. SE
Minneapolis MN 55455
golzarian@umn.edu
612-626-5388

### Name and title of the investigator(s) and sub-investigators responsible for the trial with address and phone number(s)

Dr. Shamar Young, Department of Radiology, University of Minnesota
Dr. Michael Rosenberg, Assistant Professor of Radiology, University of Minnesota
Dr. Prashant Shrestha, Assistant Professor of Radiology, University of Minnesota

### Name and addresses of the clinical laboratories and/or other institutions involved in the trial

University of Minnesota Academic Health Center
Department of Radiology
MMC 292
420 Delaware St. SE
Minneapolis, MN, 55455

Fairview-University Medical Center
500 Harvard Street SE

Minneapolis, MN 55455

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## List of Abbreviations

BPH=Benign Prostatic Hyperplasia
CFR=Code of Federal Regulations
CRF=Case Report Form
FDA=Food and Drug Administration
GCP=Good Clinical Practice
ICH=International Conference on Harmonization
IRB=Institutional Review Board
PAE=Prostatic Arterial Embolization
TRUS=Trans Rectal Ultrasonography
PVR=Post Void Residual
IPSS=International Prostate symptom score
QoL=Quality of Life
Qmax=Peak urinary flow rate
PSA=Prostate Specific Antigen

# 1 Introduction

This is an investigator-initiated application to evaluate a new prostate therapy that is intended to relieve the symptoms of Benign Prostatic Hyperplasia (BPH). There is no monetary support from commercial entities. The intent of the study is to evaluate the outcome of prostate artery embolization for treating benign prostatic hyperplasia. This procedure was originally reported from two separate groups, one in Lisbon, Portugal and one in Sao Paulo, Brazil. After their initially promising data several different groups in the United States, Asia, and Europe have added there data to the literature. The study will use commercially available embolic materials, which represents a new application for these devices, which have been cleared for sale for other indications.

# 2 BPH

## 2.1 Introduction

BPH is a highly prevalent condition in which there is nodular growth of prostatic tissue, enlarging the prostate and narrowing the urethra. BPH contributes to symptoms of frequency and urgency of urination in men as they age. It is estimated that close to 80% of men will develop BPH. Most men will be treatable for this condition with alpha-blockers or 5-alpha reductase inhibitors, but close to 10% of men who develop an enlarged prostate will need surgery to correct symptoms from this disorder. The symptoms include frequent urinary traction infections, bladder stones, inability to urinate**,** and urinary incontinence.

## 2.2 Signs and symptoms of Prostate Gland Enlargement

- Weak urine stream, difficulty in starting urination
- Stopping and starting while urinating, dribbling at the end of urination
- Straining while urinating, frequent need to urinate
- Prolonged urination
- Urge incontinence – involuntary leakage followed by urgency
- Increased frequency of urination at night (nocturia)
- Urgent need to urinate and not being able to completely empty the bladder
- Blood in the urine (hematuria)
- Urinary tract infection

## 2.3 Traditional management

### 2.3.1 Medical

Current medical management of BPH includes two class of medications that target the dynamic and stable aspects of prostatic obstruction; α-adrenergic blockers and 5α-reductase inhibitors respectively. The α-adrenergic blockers directly inhibit sympathetic tone, which relaxes the smooth muscle of the prostate. The 5α-reductase inhibitors (including Finasteride) prevent conversion of testosterone to dihydrotestosterone, which

is the chief hormone promoting stromal and epithelial proliferation in the prostate. Over the course of a year, this can decrease peri-urethral prostate size and relieve obstruction.

Anti-cholinergics are another class of medications used to ameliorate lower urinary obstructive symptoms. The urinary bladder contracts when muscarinic receptors on smooth muscle are stimulated by acetylcholine. While these drugs do not benefit patients with symptoms secondary to BPH, some of these patients may in fact have co-incident bladder dysfunction and anticholinergic medications may prove beneficial [1].

### 2.3.2 Surgical

Surgical therapy is reserved for patients exhibiting moderate to severe symptoms not controlled by medical therapy or in patients who refuse or do not tolerate medical treatment. Traditionally open prostatectomy was the surgical option of choice, but with onset of new surgical techniques and technologies open prostatectomy is typically reserved for larger (usually >80-100g) prostates. Open prostatectomy may also be recommended when there is a concomitant bladder diverticulum or bladder stone.

The current gold standard of medical refractory BPH is transurethral resection of the prostate (TURP). This procedure focuses on resecting peri-urethral prostatic tissue, which is most contributory to static obstruction. Complications of TURP include significant bleeding (often requiring transfusions), TUR syndrome (hyponatremia secondary to absorption of hypotonic irrigation), retrograde ejaculation, impotence, and urinary incontinence. Given these potentially serious adverse events, several new techniques have been developed and investigated. However, a recent systematic review noted that there is little evidence that any of these are more efficacious than TURP and as such it remains the gold standard [2]. Some of these newer approaches include transurethral incision of the prostate, which is reserved for men with obstruction and a small prostate. This procedure is more rapid than TURP and outcomes in well-selected patients are equivalent to that of TURP with less morbidity from bleeding, TUR syndrome, and rate of retrograde ejaculation [3]. Several different protocols using laser surgery for the prostate have been described, the two main energy sources are Nd:YAG and holmium: YAG. These procedures can be performed under direct visualization or with transrectal ultrasound guidance. Laser ablation is particularly useful in patients on anticoagulation as the risk of bleeding is minimal. Similar to other coagulative techniques, the prostatic urethra is not immediately excised/resected; instead it is sloughed off over the course of a few weeks. Studies suggest that patients undergoing Holmium laser enucleation require shorter hospitalization, experience decreased blood loss, and have similar outcomes to TURP at the expense of increased procedure time [4]. Yet, despite these considerable attempts at innovation in the field, none of these technologies has been sufficiently effective to displace TURP.

# 3 Report of Prior Transarterial Pelvic Embolization

## 3.1 Pelvic Embolization

Non-selective hypogastric artery embolization was originally described as a management option for refractory hematuria in 1974 [5] and was subsequently reported in case reports as an emergency treatment for refractory hematuria secondary to BPH, adenocarcinoma of the prostate, and post-operative/post-biopsy bleeding [6,7].

Over the past 3 decades there have been a number of case reports and small case series that have been published regarding embolization of pelvic tumors, including prostate and bladder cancer, and for bleeding after transurethral resection of the prostate. In total, there are 130 patients reported in the case reports and studies [5-17]. All were pelvic embolizations, with a wide range of pathologies. If one leaves out the study by Liguori [16], which included a variety of malignancies in the pelvis, all the other above cases, 86 in total, were for treatment of bleeding from the urinary tract due either to malignancy of the bladder or prostate or from bleeding after transurethral resection of the prostate. The use of a variety of embolics in these reports, in the setting of emergency treatment, without reported injury to the bladder or other pelvic organs suggests that there may be a margin of safety in the embolization of the prostate and bladder

## 3.2 Animal Studies of Prostate Embolization

Several studies have since been performed to assess the safety and feasibility of prostatic embolization in animal models.

Darewicz in 1980 [19] published the first investigation on transarterial prostatic embolization. Five dogs were catheterized and each internal iliac artery embolized with n-butyl-2-cyanoacrylate. This liquid embolic material results in complete occlusion of the vessels into which it is injected. After animal sacrifice, pathologic examination of the prostate tissue showed no macroscopic changes. Microscopic examination revealed infiltration of lymphocytes, histiocytes, and fibroblasts in the interstitial tissue. No injuries to other pelvic organs were noted.

Sun et al [20] used pigs to evaluate transcatheter arterial embolization (TAE) as a potential treatment for BPH. Sixteen healthy large white male pigs were used in this study. Eight animals were randomly assigned to the TAE group, and eight were randomly assigned to the control group. Each pig in the TAE group underwent bilateral super selective catheterization of the prostatic branch of the inferior vesical artery and subsequent embolization with 500–700 μm microsphere particles (Embosphere; Biosphere Medical, Louvres, France). Three months after the procedure, both the pigs in the TAE group and those in the control group underwent testing of their sexual function with female pigs in estrus. The pigs were then sacrificed, and necropsy and pathologic analysis were immediately performed with particular attention paid to the prostate. There was no significant difference in sexual function between the two groups. The urinary bladder, ureters, deferent ducts, urethra, sigmoid colon, and rectum appeared to be normal in all animals. The prostate volume was significantly smaller ($P<.001$) in the TAE group than in the control group. In the TAE group pigs, microsphere particles were identified within occluded arterioles and there was fibrotic tissue formation and glandular

atrophy.

In a study of prostate embolization in canines, benign prostatic hyperplasia was induced using hormones in 9 beagle dogs [21]. The dogs underwent hormonal stimulation for either 12 or 24 weeks. Five of the 9 beagles were embolized, in all cases with 255-355 μm polyvinyl alcohol (PVA) particles, (Contour®, Boston Scientific, Natick, MA). Half the dogs were hormonally stimulated for 12 weeks and half for 24 weeks. All animals that were embolized (5 of the 9) were treated 12 weeks after the initiation of the hormones and were sacrificed 12 weeks after embolization (24 weeks after baseline). In the group stimulated for 24 weeks that were not embolized, there was evidence histologically of diffuse glandular hyperplasia with micro-cystic change. Those stimulated for 24 weeks who were embolized showed gross evidence of cystic change and microscopically atrophied glands intermixed with islands of normal glandular hyperplasia. The embolic material was found in the periphery of the gland with inflammatory cell infiltration. Pathologic examination of the bladders showed one specimen with focal hemorrhage in the bladder wall, but not involving the entire thickness of the bladder. No other bladder injuries were reported.

The most recent study reported in 2011, again using hormonal stimulation in 10 beagles for 4 months [22]. Seven of the ten were randomly selected for embolization with 300-500 μm tris-acryl gelatin microspheres (TAGM). The pathologic findings were similar to the study reported above. The embolized prostate glands showed gross cystic change and microscopic cysts lined with atrophied glands, compatible with major areas of glandular necrosis. There were no bladder injuries, but two animals were found to have a slight adhesion between the posterior surface of the prostate and the anterior wall of the rectum. No mural or mucosal injuries to the rectum were reported.

Animal studies in this setting have limitations. The beagle model does not replicate human BPH, symptom change cannot be assessed in animals, and objective improvement of urinary flow also cannot be measured, as the BPH model in canines does not induce bladder outlet obstruction. Also, most men who would be treated with this treatment are over 60 and many will have atherosclerosis. It is unclear if atherosclerosis limits collateral flow to the pelvic organs and what role this might play in bladder or rectal injuries. Therefore, while the animal studies provide useful data regarding tissue response and safety of embolization, human studies are needed to further clarify safety and effectiveness.

### 3.3 Prostate embolization as a therapy for BPH in humans

In 2000 DeMeritt reported a case describing selective prostatic embolization utilizing 150-200 μm PVA particles in a 76-year-old patient with refractory hematuria and severe lower urinary tract symptoms (LUTS) secondary to BPH [23]. The gross hematuria resolved immediately after the procedure and follow-up at 12 months demonstrated a significant reduction in his LUTS as measured by the international prostate symptom score (IPSS) (24 to 13). Further, there was a 40% reduction in prostate volume and a decrease in

prostate specific antigen (PSA) from 40 ng/ml to 4 ng/mL. Aside from a transient post-operative fever, there were no complications in that patient.

In the last five years there have been several small clinical trials on patients with BPH refractory to medical management. In Brazil, Carnevale et al. performed PAE with 300-500 μm TAGM on two patients with acute urinary retention secondary to BPH who were initially managed on α-blocker therapy and urethral catheterization [24]. One patient was treated with bilateral embolization while the other was unilaterally embolized. Preliminary results with 6-month follow-up demonstrated a 39.7% reduction on US and 47.8% reduction on MRI in prostate volume from baseline in the bilaterally treated patient and 25.5% and 27.8% respectively in the unilaterally treated patient with no evidence of complications in either patient. Further follow-up at 18 months demonstrated interval increase in prostate size as measured by US and MRI in the unilaterally treated patient (19.6% and 12.2% reduction from baseline) while the bilaterally treated patient's prostate volume remained stable (39.7% and 53.6% reduction from baseline) relative to 6-month follow-up. Both patients reported significant improvement in their IPSS and quality of life (QoL) score at 18 months with the bilaterally treated patient reporting a score that decreased from 8 at 1 month follow-up to 1 while the unilaterally treated patient reported a decrease from 17 to 7 [25].

This group presented results in a total of 12 patients, including the two discussed above, at the March 2012 Annual Meeting of the Society of Interventional Radiology [26]. All of these patients had catheter dependent urinary retention. The procedure was clinically successful in 10 patients. Patients had spontaneous urination after catheter removal a mean of 12 days post-treatment. While no major complications were noted, 3 of 12 had minimal rectal bleeding, 2 of 12 had diarrhea, and focal bladder ischemia in 1 of 12. Mean prostate volume reduction was 30% and most had significant improvement in IPSS and QoL scores.

Finally, this group recently published results from a prospectively collected group of 35 patients who had very large prostates (>90 g) which ranged in size from 90-252 g [27]. This is a subset of patients that would typically require total prostatectomy. They achieved technical success, defined as bilateral prostatic artery embolization, in 33 of 35 patients. In their report of 3 month follow up the mean prostate size decreased significantly ($p < 0.001$), QoL scores improved significantly ($p < 0.001$), peak flow rate (Qmax) increased significantly ($p < 0.001$), and IPSS improved significantly ($p < 0.001$). They also demonstrated a significant decrease in the PSA ($p = 0.002$). They did have minor complications in a few patients which included two cases of rectal bleeding, two cases of hematosperima, one case of diarrhea, and one case of ureteral trauma secondary to Foley insertion.

Pisco et al. published a clinical study with 15 patients performed in Portugal in early 2011 utilizing 200 μm non-spherical PVA particles (Cook Inc., Bloomington IN) [28]. Technical success, defined as selective prostatic arterial embolization of at least one pelvic side, was achieved in 14 of 15 patients. Bilateral embolization was achieved in 13 patients, unilateral in 1 and embolization failed technically in one patient on both sides due to

vessel tortuosity. With a mean follow-up of 7.9 months Pisco et al. reported a decrease of IPSS by a mean of 6.5 points (p=.005), improved QoL score by 1.14 (p=.065), an increase in erectile function score by 1.7 points (p=0.63), a mean decrease in PSA by 2.27 ng/mL (p=.072), and a mean prostate volume reduction by 26.5 mL (p=.0001). The authors reported a major complication in one patient that experienced severe intraoperative pain during embolization and was subsequently found to have a 1.5 $cm^2$ area of necrosis in the inferior bladder wall requiring surgical repair. Of the 14 patients that were technically successfully treated, only 10 achieved clinical success (defined as an improvement of symptoms with an IPSS <20 and/or improvement of Qmax to greater than 7mL/sec).

Pisco's group also presented the results of 152 patients at the same SIR meeting in March 2012 [29] with a subset of these patients being published in early 2013 [30]. However, later in 2013 the group published their largest patient series of 255 patients. Of these patients the procedure was technically successful in 250 (98%) of patients. The group presented data for follow up at 1, 3, 6, 12, 18, 24, 30, and 36 months for varying numbers of patients. They found clinical improvement in 81.9% 80.7%, 77.9%, 75.2%, 72%, 72%, 72%, and 72% respectively. They also demonstrated statistically significant improvement of IPSS, QoL score, Qmax, PVR, prostate volume, and PSA at all time intervals. The group reported only one major complication, the afore mentioned bladder wall ischemia. They reported urinary tract infections in 19 patients, transient hematuria in 14 patients, rectorrhagia in 6 patients, and balanitis in 4 patients.

Recently, a report of early findings from a prospective United States clinical trial to evaluate the efficacy and safety of PAE for BPH has been published [32]. 72 patients were screened and 20 patients underwent treatment. Embolization was technically successful in 18 of 20 patients (90%); bilateral PAE was successful in 18 of 19 (95%). Unsuccessful embolization were secondary to atherosclerotic occlusion of prostatic arteries. Clinical success was seen in 95% of patients (19 of 20) at 1 month, with average AUA symptom score improvements of 10.8 points at 1 month (P= .0001), 12.1 points at 3 months (P = .0003), and 9.8 points at 6 months (P = .06). QoL scores improved at 1 month (1.9 points; P = .0002), 3 months (1.9 points; P = .003), and 6 months (2.6 points; P = .007). Sexual function improved by 34% at 1 month (P = .11), 5% at 3 months (P = .72), and 16% at 6 months. (P= .19). Prostate volume at 6 months had decreased 18% (n = 5; P = .05). No minor or major complications were reported.

Kubatov et al [33] also reported similarly good mid-term outcomes of 88 patients treated in Italy. They too showed a significant improvement in mean IPSS ($p < 0.05$), mean Qmax ($p < 0.05$), post void residual (PVR) ($p < 0.05$), prostate volume ($p < 0.05$), and QoL score ($p < 0.05$) at 12 months. They experienced no complication rates either minor or major as defined by the society of interventional radiology reporting standards

A randomized prospective study has evaluated the effect of different particle size (100-μm vs 200-μm) on the outcome of PAE on BPH. No significant differences were found in pain scores and adverse events between two groups. Whereas PSA level and PV showed

greater reductions after PAE with 100-μm PVA particles, clinical outcome was better with 200-μm particles. [34]

Recently Wang et al published a study of 117 patients with prostrates >80 mL in Chinese patients. They used 50 μm and 100 μm PVA [35]. They were technically successful, defined as unilateral or bilateral prostatic artery embolization, in 109 of 117 patients. This group reported outcomes at 24 months in 84 patients which demonstrated significantly decreased IPSS ($p < 0.001$), QoL scores ($p < 0.01$), Qmax ($p < 0.01$), PVR ($p < 0.01$), and decreased prostatic volume ($p < 0.01$). Some of these patients were followed for longer than 24 months after which there clinical improvement remained. This group reported no major complications with a small number of minor complications noted. The most common minor complication was urethral burning.

In early 2014 a prospective trial comparing TURP to PAE was conducted and published which demonstrated that while initially the TURP cohort showed significantly better improvement in IPSS, QoL scores, Qmax, and PVR at 1 and 3 months [36]. These differences disappear and the treatments become equivalent at 6 months and they remained equivalent at 12 and 24 months. This is consistent with the expected course as time for the prostatic tissue to become necrotic and retract is required. This study demonstrated significantly more adverse events in the PAE group than the TURP cohort. However, this group seemed to miss classify post embolic syndrome as an AE instead of an expected outcome and did not report any incontinence, impotence, or retrograde ejaculation in the TURP cohort. The lack of expected AEs in the TURP cohort, which is inconsistent with all other published data sets, have lead several authors to question the validity of the study.

Finally, we retrospectively reviewed the outcomes of our first 15 patients with symptomatic BPH treated at University of Minnesota. Our initial experience showed a technical success and clinical improvement based on IPSS of 90% and 75% respectively. Following PAE, 2 out of 15 patients had hematuria; however, post-embolization cystoscopy showed no bladder ulceration or abnormalities. These patients had a good clinical outcome in the follow up. Using Cone-Beam CT (CBCT) has allowed to identify all the collateral and dangerous anastomosis and prevented from non-target embolization.

These initial reports suggest that prostate embolization is safe. The results suggest that improvement in symptoms occurs in the majority of the patients and that shrinkage in prostate volume is likely. Only 1 major complication has been reported at this early stage. Even though it is unclear the incident of minor injuries to the bladder and rectal mucosa, based on the previous published data and our own personal experience, with the addition of CBCT, the incidence of clinically relevant complications are extremely rare. The materials used in these procedures have FDA clearance for other indications and are readily available for interventionalists to use in this treatment. The relevant clinical articles are included in Appendix G. The animal studies and the clinical studies related to prostate embolization as a treatment for BPH are provided. The studies and case reports related to the treatment of bladder or prostate hemorrhage can be provided if needed.

## 3.4 Risk/Benefits

With the proposed procedure there are the general theoretical risks associated with all angiographic procedures, which include pain, post procedure groin hematoma, bruising or bleeding at the puncture site, pseudoaneurysm, transient or permanent renal injury, arterial dissection or thrombosis (very rarely necessitating amputation), infection, fever, and a potential for an allergic reaction to intra-arterial contrast administration. Some of these complications can lead to the need for surgical intervention, new endovascular procedure, or even potentially death.

Specific risks to PAE are limited and include migration or non-selective delivery of the embolic agent leading to a non-targeted distribution. The most severe result of this could include focal necrosis of a segment of the bladder wall. They may have persistent urinary retention or incontinence. The patient may also have abdominal pain and although never reported may theoretically develop sensory abnormalities.

## 3.5 Rationale

Current “gold standards” for treatment of BPH include reducing prostate mass through either an open or robotic simple prostatectomy or transurethral resection of prostate (TURP). These are not without their own set of complications and risks. Known complications include erectile dysfunction, incontinence, bladder neck contractures, hematuria, retrograde ejaculation, etc. Estimates are as high as 1 in 5 (20%) will have a surgically related complication.

It is anticipated that PAE, if successful, will offer at least equivalent results with a markedly decreased risk profile and fewer complications, enhancing patients’ lives and health.

## 3.6 Trial Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

## 3.7 Population

- Male patients > 45 years old
- Diagnosis of BPH with moderate to severe lower urinary tract symptoms refractory to medical treatment for at least 6 months
- Currently has or willing to accept the risk of sexual dysfunction
- PSA which meets one of the following criteria:
    - Baseline PSA ≤ 2.5ng/mL
    - Baseline PSA > 2.5 ng/mL and ≤ 10 ng/mL AND free PSA ≥ 25% of total PSA (no biopsy required);

  - Baseline PSA > 2.5 ng/mL and ≤ 10 ng/mL AND free PSA < 25% of total PSA AND negative prostate biopsy result (minimum of 12 core biopsy) within 12 months;
  - Baseline PSA >10 ng/mL AND negative prostate biopsy result (minimum of 12 core biopsy) within 12 months;
  - Negative prostate biopsy (minimum 12 cores within 12 months) if abnormal digital rectal examination.
- Prostate measured volume >40 mL
- And one of the following
  - IPSS > 12
  - QoL >= 3 and up
  - Qmax, <15 mL/S
- Acute urinary retention
- Patients without prostate or urethral cancer
- Patients without New York Heart Association Class III (moderate), or higher cardiac dysfunction
- Patients without a history of recurrent urinary tract infections (>2/year), prostatitis, or interstitial cystitis.
- Patients without medically refractive hypersensitivity to contrast material
- Patients who are not willing to stop narcotic analgesia, androgen therapy, or GNRH (gonadotropin-releasing hormone) analogue therapy for 2 months prior to therapy.
- Patients with glomerular filtration rates less than $40\text{mL/min/1.73 m}2$ who are not already on dialysis
- Patients who haved used anithistamines, anti-convulsants, and antispasmodics within one week of treatment unless they have been treated with the same drug (at the same dosage) for at least 6 months and has an associated stable voiding pattern.
- Patients with a life expectancy greater than 1 year
- Patients where embolization is possible distal to collateral vessels feeding non-prostatic tissue
- Patients who have not had a prostatectomy
- Patients who do not have bilateral internal iliac artery occlusion
- Patients who do not have major neurologic illnesses which could have symptoms that may be similar to or confused for BPH (eg Parkinson's disease, multiple sclerosis, Shy-Drager syndrome, spinal cord injury, etc.).
- Patients who have not started or changed their dosage of alpha blockers or 5-alpha reductase inhibitors in the month prior to PAE
- Patients who are willing to maintain the same dosage of (or not begin if not currently taking) alpha blockers or 5-alpha reductase inhibitors throughout the study period unless absolutely medically necessary to change it.
- Patients who do not have urethral stents

# 4 Trial Objectives

The purpose of the trial is to determine the clinical outcome of Prostate Artery Embolization in the treatment of symptomatic BPH.

# 5 Trial Design

## 5.1 Primary Study Endpoints/Secondary Endpoints

The primary endpoints are adverse events, changes in symptom score as measured by IPSS, QoL score, and patient-reported change in medication use for prostate symptoms. Medical Therapy of Prostatic Symptoms (MTOPS) composite variable symptom score >30 and/or flow rate change of >15 ml/second.

## 5.2 Study Design/Type

This is a prospective cohort study without matched controls. It is a preliminary pilot study for clinical outcome that will be used to develop a larger prospective randomized study. 100 subjects will be enrolled, to reach a goal of 50 treated, and followed for one year after PAE. The patients will complete an informed consent and be enrolled prior to any study related testing taking place, for this reason it is felt a significant number of patients will not ultimately meet inclusion/exclusion criteria and thus not proceed to PAE.

## 5.3 Inclusion Criteria

- Male, 45 years or older
- Patients with a life expectancy greater than 1 year
- Currently has or willing to accept the risk of sexual dysfunction
- Diagnosis of Lower Urinary Tract Symptoms from Benign Prostatic Hyperplasia refractory to medical therapy for at least 6 months.
- IPSS score at initial evaluation should be greater than 12, and uroflowmetry (Qmax) of <15mL/s (milliliters per second).
- QoL >= 3 and up
- All prostate volumes will be > 40mL
- PSA which meets one of the following criteria:
    - Baseline PSA ≤ 2.5ng/mL
    - Baseline PSA > 2.5 ng/mL and ≤ 10 ng/mL AND free PSA ≥ 25% of total PSA (no biopsy required);
    - Baseline PSA > 2.5 ng/mL and ≤ 10 ng/mL AND free PSA < 25% of total PSA AND negative prostate biopsy result (minimum of 12 core biopsy) within 12 months;
    - Baseline PSA >10 ng/mL AND negative prostate biopsy result (minimum of 12 core biopsy) within 12 months;
    - Negative prostate biopsy (minimum 12 cores within 12 months) if abnormal digital rectal examination.
-

## 5.4 Exclusion Criteria

- Patients with active urinary tract infections or recurrent urinary tract infections (> 2/year), prostatitis, or interstitial cystitis.
- Cases of biopsy proven prostate, bladder, or urethral cancer.
- IPSS score at initial evaluation less than 12
- QoL < 3
- Patients on long-term narcotic analgesia, androgen therapy, or GNRH (gonadotropin-releasing hormone) analogue therapy who are unwilling to stop therapy for 2 months prior to the study.
- Use of anithistamines, anti-convulsants, and antispasmodics within one week of treatment unless they have been treated with the same drug (at the same dosage) for at least 6 months and has an associated stable voiding pattern.
- Patients who are classified as New York Heart Association Class III (Moderate), or higher, have cardiac arrhythmias, have uncontrolled diabetes, or are known to be immunosuppressed.
- Hypersensitivity reactions to contrast material not manageable with prophylaxis.
- Patients with glomerular filtration rates less than 40 who are not already on dialysis
- Prostate volume <40 mL
- Patients with bilateral internal iliac arterial occlusion
- Patients with causes of bladder obstruction not due to BPH (eg urethral stricture, bladder neck contraction, etc)
- Patients with neurogenic or bladder atonia
- Prior prostatectomy
- Cystolithiasis within the last 3 months
- Patients interested in future fertility
- Is not willing to accept the risk of sexual dysfunction
- Patients with a life expectancy less than 1 year
- Patients where embolization is not possible distal to collateral vessels feeding non-prostatic tissue
- Patients with major neurologic illnesses which could have symptoms that may be similar to or confused for BPH (eg Parkinson's disease, multiple sclerosis, Shy-Drager syndrome, spinal cord injury, etc.).
- Patients with urethral stents
- Patients who have undergone prior rectal surgery other than hemorrhoidectomy or pelvic irradiation.
- Patients who have started or changed their dosage of alpha blockers or 5-alpha reductase inhibitors in the month prior to PAE
- Patients who are unwilling to maintain the same dosage of (or not begin if not currently taking) alpha blockers or 5-alpha reductase inhibitors throughout the study period unless absolutely medically necessary to change it.

## 5.5 Pre-procedure Patient Evaluation

The pre-procedure evaluation will be billed to patients or their insurers. Some of the tests are typical for benign prostatic hyperplasia work up while others are not. The

patient will be informed of the possible cost not covered by insurance at the time of informed consent.

Subjects will undergo pre- and post-embolization evaluation consisting of
PSA test — if this is abnormal, subjects will be asked to have a prostate biopsy if one has not been obtained. PSA test is at 3 month follow up. This is a blood test requiring about 1 teaspoonful of blood.

Comprehensive chemistry and CBC blood tests, and a urinalysis pre and at 3 month
TRUS to measure prostate volume pre – and post-embolization

Uroflowmetry measures the flow dynamics of urine released from the body, the speed with which it is released, and how long the release takes. The “post-void residual” is an ultrasound test to measures the amount of urine remaining in the bladder after urination.
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Symptom scores, global quality of life, and IPSS questionnaires.

MRI/MRA to evaluate the prostatic arteries, and assess the prostate gland perfusion. It also allows measurement of the size and the morphology of the prostate before embolization. If the patient is unable to have an MRI, then a CTA of the prostate should be performed.

Cystoscopy — a test to look inside the bladder with a type of scope to see if there is abnormalities inside the bladder.

Urine Culture: This will be performed prior to embolization to ensure the patient does not have a UTI. It will be repeated as needed if signs or symptoms of UTI arise.

**5.5.5 Follow up evaluation**
At 1 month after PAE, subjects will be evaluated for adverse events and their medical history will be updated. They will also have cystoscopy, uroflowmetry, and QoL/IPSS questionnaires. The patients will also have pain evaluated by the revised faces pain scale.

At 3 months after PAE subjects will be evaluated for adverse events and their medical history will be updated. They will also have labs, TRUS*, uroflowmetry, IPSS/QoL, and CT or MR imaging. The patients will also have pain evaluated by the revised faces pain scale.

At 6 after PAE subjects will be evaluated for adverse events and their medical history will be updated. They will also have IPSS/ QoL questionnaires performed. The patients will also have pain evaluated by the revised faces pain scale.

At 12 months after PAE subjects will be evaluated for adverse events and their medical history updated. They will also have uroflowmetry, IPSS/QoL questionnaires performed. Additionally, they will have pain evaluated by the revised faces pain scale.

The International Index of Erectile Function (IIEF-5) Questionnaire is a validated, gender-specific measure of sexual function assessed at each follow-up visit

*At time of TRUS the patients' anus/rectum will also be evaluated. This will be done by using the ultrasound to evaluate the anus/rectal wall by adjusting the ultrasound depth and turning the ultrasound in a complete circle.

### 5.6 Description of the Device

We plan to use Three embolic materials, cleared for use by the FDA for other uses. It is listed below, along with the regulatory reference files. The letters confirming these reference files are provided in Appendix B. The embolics will be used to perform PAE. The materiasl we plan to use Embosphere® and Embozene™ particles that are commercially available and have been used for several years.

1. Embosphere Particles, Merit Medical (Rockland, MA).
2. Embozene Particles, Boston Scientific (Marlborough, MA).

### 5.7 Principle of operation of the devices

These materials are designed for intra-arterial injection and provide mechanical occlusion of the vessels distal to the injection site. The spheres or particles are carried by the arterial flow forward and wedge in the vessel once they reach a small enough diameter. The materials are permanent occlusive agents, in that they are not resorbed and are scarred into the vessel. The vessel occlusion causes ischemia in the tissue supplied by those vessels and in particularly sensitive tissue, such as fibroids, the ischemia results in infarction of the tissue. It appears that at least a portion of the hyperplastic tissue in the prostate also infarcts (based on non-perfusion on contrast-enhanced MRI studies) and that results in volume reduction, presumed to be associated with an in improvement in lower urinary tract symptoms.

### 5.8 Anticipated changes in the devices

No changes will be made in these devices.

### 5.9 Pre-procedure Patient Evaluation

The pre-procedure evaluation is standard of care and will be billed to patients or their insurers. Laboratory analysis of PSA, hemogram and urinalysis; trans-rectal ultrasound (TRUS) for prostate volume at which time the anus and rectum will be evaluated, cystoscopy and uroflowmetry will be done in urology. A CT or MR perfusion imaging exam will be done in radiology. This is the standard evaluation for benign prostatic hyperplasia. Clinic visits with both an urologist and interventional radiologist will complete the pre-PAE evaluation.

### 5.10 Procedure

Subjects will be scheduled in Interventional Radiology for a PAE consult after they complete a urologic evaluation including TRUS, uroflowmetry, cystoscopy, and laboratory analyses. The IR clinic consult will include screening for eligibility, informed consent, IPSS, QoL, and IIEF questionnaires as well as a consult appointment with the Principal

Investigator. The PI's coordinators and Urology coordinators will collaborate regarding the subject study calendar.
Consented subjects will have prostate embolization.

- The morning prior to the procedure the patient will be given ibuprofen and Omeprazol. The patient will be given ciprofloxacin just prior to the procedure.
- Under US guidance right common femoral arterial access will be achieved using micropuncture technique and micropuncture needle ultimately exchanged for a 5 Fr introducer sheath.
- The left internal iliac artery will be catheterized using an appropriate catheter. A co-axial microcatheter system will be advanced into the anterior branch of the internal iliac artery and angiograms obtained.
- The catheter will then be selectively advanced into likely inferior vesical artery and microcatheter injections performed to identify and catheterize the prostatic artery. A CBCT may be performed at this stage. CBCT is optional and will be used in cases where the provider feels that further spatial resolution is needed to avoid embolizing from a point that would cause non-target embolization. This will be weighed against the increased radiation that comes with CBCT.
- The microcatheter will then be positioned as distally as possible and CBCT study obtained to map the prostatic branches.
- Once catheter position is confirmed embolization will be performed using Embosphere or Embozene particles of a size to be decided by the interventional radiologist at the time of procedure.
- Recheck images will demonstrate good-coverage of the small prostatic branches.
- At this point the right will be studied after catheterization of the left internal iliac artery using an appropriate catheter and angiograms obtained.
- The microcatheter will be advanced into the prostatic branches and microcatheter injections performed.
- Again a small fraction of microparticles will be injected with adequate coverage of vascular branch with preserving the bladder vascularity as much as possible.
- The above process will be repeated on the contralateral side resulting in a bilateral embolization.
- Hemostasis at the arterial puncture will be achieved using a closure device followed by gentle manual compression.

# 6 Assessment of Efficacy

## 6.1 Efficacy Parameters

The primary efficacy parameters are symptoms improvement as measured by IPSS and QoL scores and change in uroflowmetrics. The primary clinical endpoint is Qmax at 3 months. The primary endpoint will be reported after all subjects have completed 3 months of follow-up.

## 6.2 Method and Timing

Imaging, labs, uroflowmetry, and questionnaires will be completed prior to embolization but within 12 weeks of the procedure. Each follow up visit will be performed at the

specified time plus/minus 2 weeks (eg 1 month +/- 2 weeks). This will help to determine the optimal follow-up timing for the larger randomized trial to follow.

Table 1. Study-specific procedures

| | Pre-embolization | PAE treatment | 1 Month | 3 Months | 6 Months | 12 Months |
|---|---|---|---|---|---|---|
| Labs: PSA, CBC, UA | **Insurance** IR clinic | | | **Insurance** IR clinic | | |
| TRUS prostate volume* | **Insurance** Urology | | | **Insurance** Urology | | |
| **Cystoscopy | **Insurance** Urology | | **Research** Urology | | | |
| Uroflowmetry -Qmax, PVR | **Insurance** Urology | | **Insurance** Urology | **Insurance** Urology | | **Insurance** Urology |
| IPSS,QOL, IIEF-5 | **Research** IR clinic | | **Research** IR clinic | **Research** IR clinic | **Research** IR clinic | **Research** IR clinic |
| Prostate Artery Embolization | | **Research** IR | | | | |
| CTA/MR perfusion | **Insurance** Radiology | | | **Insurance** Radiology | | |
| Adverse event assessment | **Research** IR clinic | **Research** IR | **Research** IR clinic | **Research** IR clinic | **Research** IR clinic | **Research** IR clinic |
| Med HX | **Research** IR clinic | | **Research** IR clinic | **Research** IR clinic | **Research** IR clinic | **Research** IR clinic |
| Pain Scale | | | **Research** IR clinic | **Research** IR clinic | **Research** IR clinic | **Research** IR clinic |

*The anus and rectum will also be evaluated at TRUS. Anoscopy will be performed if abnormalities are seen at TRUS and/or if there is blood in the stools or concerning symptomatology.
** Cystoscopy may be performed sooner or more frequently if there is hematuria and if the cystoscopy shows abnormalities after the procedure.

The initial evaluations (new patient IR clinic visit, labs, urologic evaluations) are required for assessment of inclusion criteria and will be billed to the patient or their insurance in the usual manner. After enrollment in the study, the evaluations will be billed to the study. Coordinators in Interventional Radiology and Urology will work together to keep subjects on calendar.

*Prostate volume:* We want to know if PAE can reduce prostatic volume. An increase in prostatic volume can also indicate the progression of BPH. TRUS can be used to measure both prostate length and weight. TRUS is the current standard imaging for the clinical assessment of the prostate gland [35]

*Uroflowmetry:* Decreased peak urine flow rates are common in men with BPH. Uroflowmetry including peak and average flow rates, total void time, and total void volume at each follow-up visit.

*Post void residual (PVR) urine volume*: PVR has generally been considered to reflect the severity of bladder outlet obstruction. PVR will be measured at each follow-up visit to monitor impairment or improvement of bladder emptying due to the treatment or disease progression.

*CTA/MR perfusion:* Will identify the prostatic vasculature and serve as a map for the embolization procedure.

*IPSS and Quality of life*: BPH is associated with impairment of quality of life. A validated quality of life measure specific to BPH into the study includes the disease-specific quality of life question included with the AUA-SI (or IPSS) questionnaire. [38-39]

*Sexual function and dysfunction:* Both BPH and many of its therapies adversely affect sexual function. The International Index of Erectile Function (IIEF-5) Questionnaire is a validated, gender-specific measure of sexual function assessed at each follow-up visit [40].

# 7 Assessment of Safety

## 7.1 Definitions

To collect safety information reliably, all adverse events will be recorded. The anticipated adverse events include:

- Genitourinary events, i.e., events associated with the urinary tract and/or the surrounding genital region
- Damage to the bladder floor, trigone, sphincters, and rectum
- Infections
- Secondary surgical interventions
- All transient post-procedure events
- Deaths

Potential Complications of vascular embolization

Vascular embolization is a high-risk procedure. Complications may occur at any time during or after the procedure, and may include, but are not limited to, the following:

- Stroke or cerebral infarction

- Occlusion of vessels in healthy territories
- Vascular rupture and hemorrhage
- Neurological deficits
- Infection or hematoma at the injection site
- Allergic reaction, cutaneous irritations
- Transient pain and fever
- Vasospasm
- Death
- Ischemia at an undesirable location, including ischemic stroke, ischemic infarction (including myocardial infarction), and tissue necrosis

Also, the Society of Interventional Radiology complications classes will be assessed following the PAE procedure. These classes include vascular, device related, contrast related, neurologic, peripheral nervous system complications, respiratory/pulmonary, infectious/inflammatory, and death.

Adverse events will be categorized according to their respective relatedness to the device or procedure, and their severity. The onset, resolution and method of resolution will be documented.

Adverse Events (AEs) encountered during treatment and post treatment periods will be recorded on the appropriate AE pages of the Case Report Form (CRF).

For this protocol, an AE is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, abnormal laboratory finding) that begins or worsens (in severity or frequency) from baseline status during the treatment or post treatment periods. Note: Unchanged, chronic medical conditions are **NOT** AEs and should not be recorded on AE pages of the CRF unless there is an exacerbation of a chronic condition.

AEs will be classified according to NCI's common terminology criteria for adverse events V 4.0 (CTCAE) and reported on the schedule below.

A copy of the CTCAE can be downloaded from: http://ctep.cancer.gov/protocolDevelopment/electronicapplications/docs/ctcaev3.pdf

AEs should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE):

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care

ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

**Serious adverse events (SAEs)** are adverse events occurring at any dose, which meet one or more of the following **serious criteria**:

- AE resulted in **death**
- Is **life-threatening** (i.e. The AE placed the subject at **immediate** risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe.)
- Requires or prolongs inpatient **hospitalization** (i.e. The AE required at least a 24-hour inpatient hospitalization.) Elective hospitalizations are not SAEs by this criterion.
- Is **disabling** (i.e. temporary or permanent disruption in activities of daily living)
- Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a subject exposed to the study drug prior to conception or during pregnancy)
- It does not meet any of the above serious criteria but **may jeopardize the subject** and **may require medical or surgical intervention** to prevent one of the outcomes listed above. (This criterion should not be used for SAEs that meet any other seriousness criteria.)

**Unexpected Serious Adverse Events** are those that have not been described in the:

- Package insert or investigator's brochure (for FDA investigational agents);
- Protocol; or
- Informed consent document.

**Adverse Event** - Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.

**Attribution** – The determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories include Definite, Probable, Possible, Unlikely and Unrelated. A clinical events committee will make this determination.

**Unrelated**: The adverse event is clearly not related to the investigational agent/procedure. - i.e. Another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study medication administration; and/or a causal relationship is considered biologically implausible.

**Unlikely**: The adverse event is doubtfully related to the investigational agent/procedure.

**Possibly**: An event that follows a reasonable temporal sequence from administration of the study drug/procedure, follows a known or expected response pattern to the suspected drug, but that could readily have been produced by a number of other factors.

**Probably**: The adverse event is likely related to the investigational agent/procedure.

**Definitely Related**: The adverse event is clearly related to the investigational agent/procedure – i.e. An event that follows a reasonable temporal sequence from administration of the study drug, follows a known or expected response pattern to the suspected drug, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the patient's clinical state.

Figure: Summary of Expedited Reporting for Investigational Agents for Phase 1, Phase 2, and Phase 3

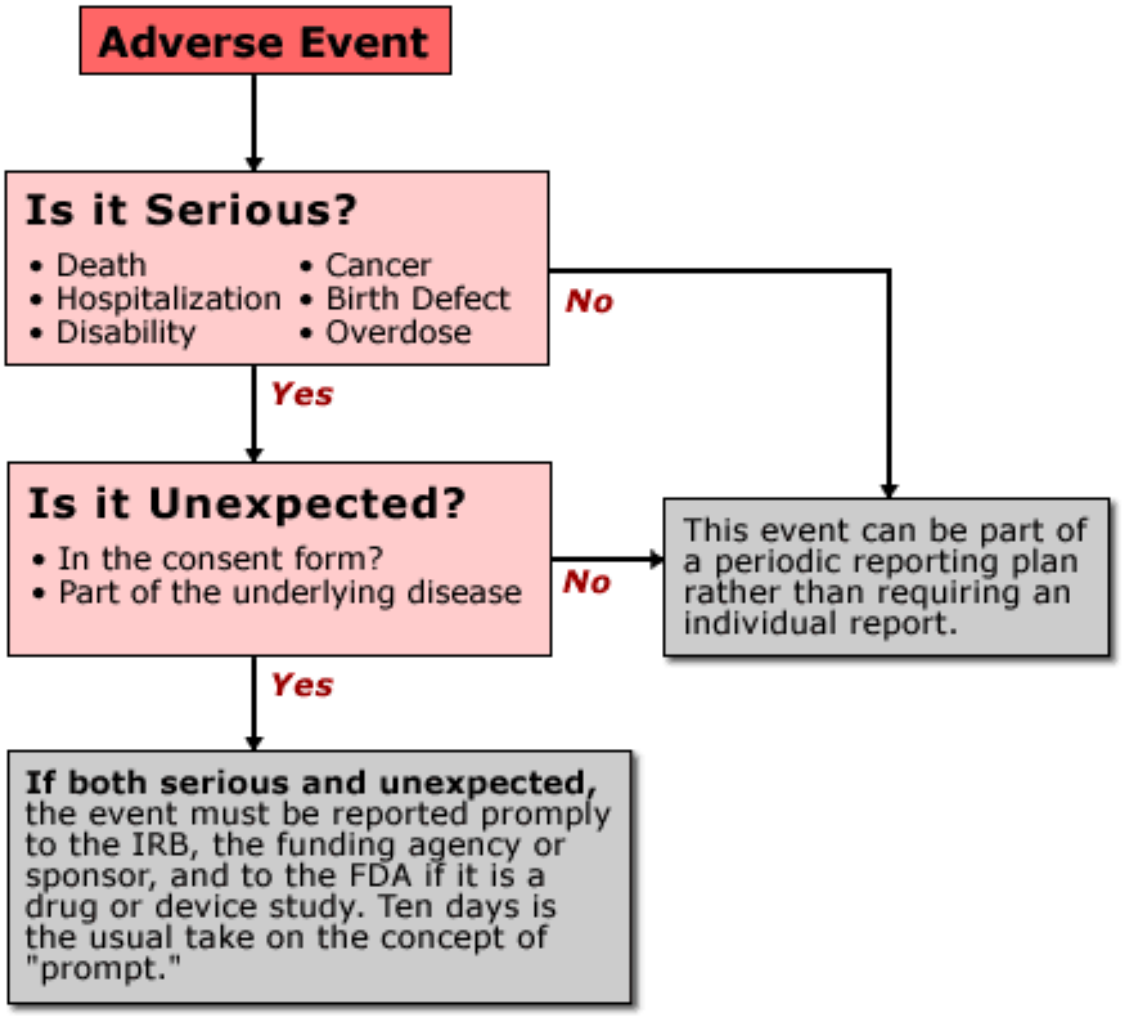


Table 2. Adverse event expedited reporting system

| Attribution | Adverse Event | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Grade 1 | | Grade 2 | | Grade 3 and/or hospitalization | | Grade 4 and/or hospitalization | | Grade 5 and/or hospitalization | |
| | Unexpected | Expected | Unexpected | Expected | Unexpected | Expected | Unexpected | Expected | Unexpected | Expected |
| Unrelated | | | | | | | | | | |
| Unlikely | | | | | | | | | | |
| Possible | | | | | | | | | | |
| Probable | | | | | | | | | | |
| Definite | | | | | | | | | | |

**Reporting: All AEs should be coded using the CTCAE V4.0**. These AEs will then be reported to the FDA in a timely manner. A Summary table will also be generated filling in the below variables:

| Variable | Number of Patients | Percentage of Patients |
|---|---|---|

| | | |
|---|---|---|
| At least one AE | | |
| At least one SAE | | |
| At least one related AE | | |
| At least one related SAE | | |
| At least one AE leading to discontinuation | | |
| At least one AE resulting in death | | |

### 7.2 Adverse Event Follow-up

All patients with adverse events will be followed up by the PI until resolution or stabilization of chronic side effects related to their adverse events has been achieved. The patients will also be referred to any applicable specialist for their expert opinion and assistance in managing/treating any adverse event. Specifically patients who develop hematuria will be referred to Urology for cystoscopy and those who develop rectal bleeding will be referred for anoscopy.

## 8 Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies. Applicable government regulations and University of Minnesota research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the University of Minnesota Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. The subject or legally acceptable surrogate must sign this consent form, and the investigator-designated research professional obtaining the consent.

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