PROSTATE EMBOLIZATION FOR BENIGN PROSTATIC HYPERPLASIA (BPH)

NCT:1924988

Approved by the Georgetown University Institutional Review Board

6/20/2013

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Georgetown University Institutional Review Board Application (Protocol) for Biomedical IRB Review (AB-1)

Section One: Application Information

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Title of Project	**Purpose of Project (one or two sentences)**
Prostate Embolization for Benign Prostatic Hyperplasia	This is a Phase I/II study with the primary goal of determining the safety of prostatic artery embolization (PAE) for benign prostatic hypertrophy. Our primary outcome is the frequency of adverse events, particularly bladder and rectal complications, which may occur as a result of this procedure. Secondarily, the study will allow us to begin to determine its effectiveness in diminishing obstructive symptoms associated with BPH.

Additional Co-Investigators/Consultants, if any	**Department or Institution**

Justin Lee, MD	Department of Radiology
Keith Kowalczyk MD	Department of Urology

Estimated duration of total project	12 month recruitment, 5 year follow-up
Estimated total number of subjects (including control subjects)	30
Age range of subjects	40 - 99
Sex of subjects	Male
Where will study be conducted?	Georgetown University Hospital
Source of subjects	Georgetown University Hospital, Depts. of Radiology and Urology
Experience of Principal Investigator: Brief summary (also attach a CV, biosketch, or Form 1572, if available)	Dr. Spies is an internationally known researcher in embolization, particularly of uterine fibroids. His group has performed over 3000 uterine embolization procedures. He has a long history in managing both single center and multi-center clinical studies in embolization. He has performed similar PhaseI1 and II studies in uterine embolization and his initial 1997 Georgetown IRB protocol for uterine embolization was the first such protocol in the country. He has long experience in safety studies, having studied the complication rates of the first 400 uterine embolization patients treated here and also as a co-investigator on the FIBROID Registry, a 3000 patient safety and efficacy registry. Dr. Spies has visited centers in both Lisbon, Portugal and Sao Paulo, Brazil and has observed approximately 20 prostate embolization procedures during those visits. He also performed a prostate embolization under the tutelage of Dr. Francisco Carnevale at the University of Sao Paulo

Source of Funding/Grant Support for Project (if any) Please attach two copies of the Grant Application	**Commercial Support (if any) for Project**
None	

Has this study undergone previous scientific review?
Please note that **independent scientific review and approval** are **required** for all **DOD** sponsored studies.

☐ Yes ☒ No

If yes, state where reviewed and attach documentation of approval

Investigational New Drug (IND)	**Investigational Device Exemptions (IDE)**
☒ None ☐ IND: FDA #_____ ☐ Drug Name: _____ ☐ Drug Sponsor: _____ ☐ Significant (SR) ☐ Non-Significant Risk (NSR)	☐None X IDE: FDA No. G120220/A00 X Device Name: Embospheres Microspheres ☐ Device Sponsor: _____Investigator sponsored_____ X Significant (SR) ☐ Non-Significant Risk (NSR)
If this project involves an FDA regulated drug or device, you must file an FDA form 3455. Please submit any communications from the FDA regarding IND, IDE, or humanitarian use applications related to this submission.	
Phase I/II **Phase: I** ☐ **II** ☐ **III** ☐ **IV** ☐ **Pilot** ☐	

Section Two: Additional Georgetown University Regulatory Information

1. Does this project involve the use of biohazardous materials, recombinant DNA and/or gene therapy? If so, Institutional Biosafety Committee (IBC) approval must be obtained. Contact (202) 687-4712 for assistance.

☐ Yes ☒ No

Has the Institutional Biosafety Committee approved the protocol?

☐**Approved**	**Date Approved**:
☐**Application Pending**	**Date Submitted**:

2. Does this project include the use of radioisotopes and/or radiation-producing devices regardless of whether the use is incidental to the project? If so, all protocols must be submitted to the GUH RSC along with a completed Form_0.30 for Radioactive or Form_0.31 for X-Rays. The forms require information on the use of radioisotopes and radiation-producing devices and must include dose calculations. Forms are on the IRB website: http://www.georgetown.edu/gumc/ora/irb/irbForms.htm or call 202-444-4657 to obtain forms or if additional information is required.

☒ Yes ☐ No

Has the Radiation Safety Committee approved the protocol?

☐**Approved**	**Date Approved**:
☒ **Application Pending**	**Date Submitted**:

3. Does this project involve the use of fetal tissue?

☐ Yes ☒ No

4. Do any investigators or co-investigators have a conflict of interest as defined in the Georgetown University Faculty handbook? http://www.georgetown.edu/facultysenate/handbook.html#financial

☐ Yes ☒ No

A copy of the current Conflicts of Interest Disclosure Form for each Investigator and Co-Investigator involved with this study must be attached to this application.

Section Three: Information for Protocol Review
Please answer each specific question and use additional sheets as needed. A response of "See attached protocol or grant application" is not sufficient.

5. Study Description (summarize the protocol according to the following format in less than 2 total pages)

Study Design (for example, hypothesis, research question, standard and experimental procedures, special or unusual equipment or procedures) **:**

This study will assess if embolization of the prostate can produce symptomatic improvement for patients with lower urinary tract symptoms as a result of benign prostatic hyperplasia. It will be managed by personnel of the Interventional Radiology Section of the Department of Radiology and members of the Urology department of of Georgetown University Hospital.

Rationale and justification for study (for example, historical background, investigator's personal experience, pertinent medical literature):

Benign prostatic hyperplasia is a highly prevalent condition in which there is nodular growth of prostatic tissue, enlarging the prostate and narrowing the urethra. It may result in symptoms of lower urinary tract obstruction including hesitancy, intermittent voiding, weakened urinary stream, incomplete emptying, and post-void leakage. The pathophysiology of BPH-induced obstruction includes mechanical and dynamic components. The mechanical component consists of tissue invasion into the urethral lumen or bladder neck. The dynamic component results from adrenergic tone on the smooth muscle within the stroma. Both these components contribute to an increase in urinary outflow resistance.

Current medical management of BPH includes two classes 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].

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 the 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 surgical options 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, TUR syndrome (hyponatremia secondary to absorption of

hypotonic irrigant), retrograde ejaculation, and urinary incontinence. Given these potentially serious adverse events, several new techniques have been developed, yet a recent systematic review noted that there is little evidence any are more efficacious than TURP and as such it remains the gold standard [2]. Some of these newer approaches include transurethral incision of prostate, which is reserved for men with obstruction and small prostates. 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 techniques of 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 bleeding risk 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.

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. These findings are summarized in the table below.

Table 1. Reports of embolization for bladder or prostate bleeding

Study	Pathology	# of patients	Embolic	Control of hemorrhage	Major Complications
Hald et al 1974 [5]	Bladder hemorrhage	1		Yes	None
Mitchell et al 1976 [6]	Prostate cancer, Post-TURP Bleeding	4		Yes	None
Russinovich 1979 [7]	Post-TURP bleeding	1	Gelfoam	Yes	None
Faysal et al 1979	Post-TURP bleeding	1		Yes	None
Appleton et al 1988 [8]	Bladder hemorrhage Prostate hemorrhage	8 bladder 2 prostate		Yes for prostate Yes for 4 of 6 bladder	None
Suzuki et al 1998 [9]	Post-TURP bleeding	1	Cyanoacrylate and coils	Yes	None
Barbieri et al 2002 [10]	Post-TURP bleeding	1		Yes	None
Michel et al 2002 [11]	Post-TURP bleeding	1	Cyanoacrylate	Yes	None
Nabi et al 2003 [12]	Prostate cancer Bladder cancer	3 prostate 3 bladder	Coils in the hypogastric artery	Yes	None
El-Assmy et al	Bladder hemorrhage	7	Alcohol and	Yes, recurrence	None

2007 [13]			microcoils	in 3	
Rastinehad et al 2008 [14]	CA of the prostate Post-TURP bleeding	6 2	PVA or TAGM	Yes, recurrence in 1 cancer patient	Rectal-vaginal fistula in cancer patient
Tan et al 2009 [15]	Post-TURP bleeding	1			
Liguori et al 2010 [16]	Cancer of bladder, prostate, uterus, other cancers	44	PVA, PVA hydrogel spheres	Yes in 81% Reduced bleeding in others	None
Delgal et al 2010 [17]	Bladder hemorrhage /Prostate hemorrhage	20	PVA or TAGM	Yes in 90%	None
Jeong et al 2010 [18]	Hemorrhage after radical prostatectomy	4	Enbucrylate and poppy oil	Yes	None

In total, there are 130 patients reported in the case reports and studies listed above. All were pelvic embolizations, although 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.

Animal Studies of Prostate Embolization

Several studies have since been performed to assess the safety and feasibility of prostatic embolization in animal models. The earliest was an investigation published in 1980 by Darewicz [19]. 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 lympohocytes, histiocytes and fibroblasts in the interstitial tissue. No injuries to other pelvic organs were noted.

A study on 16 healthy male pigs (randomly assigned to embolization or control) investigated sexual function after prostate embolization [20]. The treatment arm underwent embolization with 500-700 micron size tris-acryl gelatin microspheres (TAGM), (Embosphere® Microspheres, Biosphere Medical/ Merit Medical, South Jordan UT) of animal's prostatic arterial supply, while the control group underwent prostate arteriography alone. Sexual function was evaluated in all the pigs by observation of mating behavior 3 months after the procedure and no difference was noted between the groups ($p = 0.328$). The animals were then sacrificed and the urinary bladder, ureters, vas deferens and urethra were normal in all. The treated animals' prostate glands were smaller than the untreated (3.9 ml vs 7.3 ml, $p < 0.001$) and pathologically demonstrated arteriolar thickening with leukocytic infiltration. There was peri-arteriolar fibrosis, with atrophy of the glandular tissue in most of the balance of the gland.

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 micron size polyvinyl alcohol particles (PVA), (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.

A similar study was reported in 2011, again using hormonal stimulation in 10 beagles for 3 months [22]. Seven of the ten were randomly selected for embolization with 300-500 micron size 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.

Prostate embolization as a therapy for BPH in humans

In 2000 DeMeritt reported a case describing selective prostatic embolization utilizing 150-200μm 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 IPSS (24 to 13). Further, there was a 40% reduction in prostate volume and a decrease in PSA from 40ng/ml to 4ng/mL. Aside from a transient post-operative fever, there were no complications in that patient.

Recently there have been several small clinical trials on patients with BPH refractory to medical management. In Brazil, Carnevale et al. performed PAE with 300-500μm 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 unilaterally. 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 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 has recently presented its most recent 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.

A clinical study with 15 patients performed in Portugal was published in early 2011 by Pisco et al. utilizing 200μm non-spherical PVA particles (Cook Inc., Bloomington IN) [27]. 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 quality of life 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 2.27ng/mL (*p=.072*), and a mean prostate volume reduction by 26.5mL (*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 1.5cm^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 Q_{max} to greater than 7mL/sec).

Pisco's group also just presented the results of 152 patients at the same SIR meeting in March 2012 [28], although these results are not yet published. The procedure was technically successful in 144 of 152 patients. Follow-up of between 3 and 30 months was available in 102 patients. Clinical success was noted in 84.3% at 3 months and in 38 of 46 (82.6%) at 12 months. These authors reported no major complications beyond the bladder wall ischemia noted in their initial published report. They did report a number of minor complications, although they did not report the frequency in the published abstract. These included burning in the urethra, urinary infection, hematuria, hemospermia, balanoprostatitis, rectorrhagia, inguinal hematoma and pain.

These initial reports suggest that prostate embolization is feasible and the initial results suggest that improvement in symptoms occurs in the majority and that shrinkage in prostate volume is likely. The safety is somewhat less certain. While major complications are likely rare, it is unclear how frequently minor injuries to the bladder and rectal mucosa occur. We believe it is important to confirm the safety of this procedure in practice in a well-designed study in the US, with careful evaluation and follow-up of each patient prior to the development of a larger trial or acceptance of this procedure into practice. The materials used in these procedures have FDA clearance for other indications and are readily available for interventionalists to use in this treatment. To date there has been no clinical trial completed in the United States and we believe that an assessment of this treatment in clinical studies is essential before its adoption into practice.

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Primary study endpoint:

Frequency of complications to the bladder and rectum

Primary objective:

The primary outcome is the absence of complications to the bladder, rectum or other pelvic structures detected in the first week after therapy. Each patient will be judged free of these adverse events or not. For those with an adverse event, the complication will be scored as to severity and outcome, as defined in the adverse events section of this protocol

Secondary objectives:
Improvement in the International Prostate Symptom Score (IPSS), a validated and well-accepted symptom and quality of life questionnaire.
Improvement in the International Index of Erectile Function (IIEF-5), a validated questionnaire to assess erectile function.
Improvement in Uroflowmetry (Qmax) post embolization
Prostate volume compared to a pre and post embolization US
Serum PSA pre and post procedure
Post procedural pain as measured on a visual analogue scale (VAS).
Procedure time and radiation parameters (fluoroscopy time, dose area product, cumulative dose).
Prostate volume as determined by measurements of the gland using MRI.
Extent of devascularization of prostate tissue as estimated from contrast-enhanced MRI.

Study Plan

Objectives of the investigation
This is a Phase I-II study with the primary goal of determining the safety of prostatic artery embolization (PAE) for benign prostatic hyperplasia. Our primary outcome is the frequency of adverse events, particularly bladder and rectal complications, which may occur as a result of this procedure. Secondarily, the study will allow us to begin to determine its effectiveness in diminishing obstructive symptoms associated with BPH.

Duration of investigation
The investigation will enroll 30 patients, with a target enrollment period of less than 12 months. Each patient will be consented for follow-up up to 5 years, but each patient will reach the first important safety endpoint 1 week after treatment and the first clinical efficacy assessment 3 months after treatment.

Written Protocol

Objectives
To determine the safety and effectiveness of prostate artery embolization for the treatment of BPH.

Description of study type
This is a prospective observational non-comparative study of an initial cohort of 30 patients.

Study Population
The patients will be recruited from the urology practice at Georgetown University and from other urologists in the area and by patient self-referral. The study will be registered at clinicaltrials.gov and also will be announced on a study website, the content of which will be approved by the IRB at Georgetown University Medical Center

and both of these sites may lead patients to self-refer for participation.

Patient Inclusion Criteria

1. Men presenting with benign prostatic hyperplasia with symptoms for at least 6 months that are refractory to medical management or in whom medications are contraindicated, not tolerated or refused. Additional criteria include:
    a. Moderate to severe obstructive urinary tract symptoms as defined as an International Prostate Symptom Score (IPSS) score of 12 or greater.
    b. Peak urinary flow (QMax) of less than 12 mL/s or acute urinary retention.
    c. Prostate volume of greater than 50 cc and less than 100 cc.
    d. Minimum age of 50 years, maximum age of 90 years

Exclusion Criteria

1. Presence of prostate cancer based on digital rectal exam (DRE), biopsy, Transrectal Ultrasound (TRUS), PSA > 10 ng/mL.
2. Renal insufficiency (serum creatinine of greater than 1.8 mg/dL)
3. Prior prostate surgery or intervention, including trans-urethral resection of the prostate, balloon dilation, stent implantation, laser prostatectomy, or hyperthermia
4. Other bladder or urethral pathology requiring therapy, either in the past or currently, including neurogenic bladder, sphincteric abnormalities, bladder cancer, or other causes of bladder atonia
5. Other causes of urinary obstruction, such as strictures of urethra or ureters not related to BPH
6. History of cardiac arrhythmias, congestive heart failure, uncontrolled diabetes mellitus, significant respiratory disease, or known immunosuppression.
7. Patients with coagulation disturbances
8. Concomitant medications (use of alpha-blockers within two months, 5-alpha-reductase inhibitors within six months, anti-cholinergics within two months, and beta blockers/antihistamines/anticonvulsants/antispasmodics within one week of treatment unless there is documented evidence that the patient has been on the same drug with a stable voiding pattern)
9. Active urinary tract infection
10. Allergy to iodinated contrast agents
11. Hypersensitivity to collagen or gelatin products
12. Acute urinary retention untreated by urinary catheterization
13. PVR > 250 mL as measured by ultrasound
14. Cystolithiasis or hematuria within three months
15. Previous rectal surgery, excluding hemorrhoidectomy, or history of rectal disease
16. Prior pelvic irradiation or radical pelvic surgery
17. Known major iliac arterial occlusive disease
18. Contraindication to embolization, such as intolerance to vessel occlusion procedures, vascular anatomy/blood flow that precludes catheter placement or embolic agent injection, presence/likely onset of vasospasm, presence/likely onset of hemorrhage, severe atheromatous disease, feeding arteries smaller than distal branches, collateral vessel pathways endangering normal territories during embolization, and pelvic inflammatory disease.
19. Men interested in future fertility

Pre-procedure Patient Evaluation

Patients may present in one of 3 ways: self-referral, referral from urologists or other community physicians or referral from the Urology Department. Prior to screening for the study, potential study participant will be provided information regarding the study. The informed consent form will be given to each potential participant and consent will be obtained prior to screening.

Once patients agree to proceed and have signed a consent, they will be screened by the research coordinator for

exclusion criteria. If they are not excluded, they will be evaluated by the co-investigator urologists and the following will be done.

.

a. IPSS will be administered
b. Urine analysis, culture, sensitivity (if indicated)
c. Blood chemistry (including blood count, BUN, serum creatinine)
d. A baseline serum prostate specific antigen (PSA).
e. A focused urologic physical examination, including a rectal exam and trans-rectal ultrasound to detect prostate volume.
f. The patient will complete uroflowmetry, including voided volume (>125cc), total time of voiding, peak urine flow rate, average urine flow rate, and post-void residual volume.

If either physical examination or PSA suggests possible prostate cancer, trans-rectal prostate biopsy will be performed. If prostate cancer is detected, the patient will be excluded.

Provided participants are not excluded based on the above evaluation, at a separate visit, each will have:

a. Anoscopy and cystoscopy in the urology clinic to ensure that these are normal, without mucosal abnormality.
b. A baseline contrast-enhanced MRI of the prostate will be completed.
c. The patient will also complete a 5 question sexual function questionnaire, the International Index of Erectile Function (IIEF). This questionnaire and the IPSS are described in detail in a later section.
d. Each patient will have a consultation visit with one of the interventional radiologist co-investigators. The patient will have a focused physical examination, including vascular exam, and will have the procedure explained in detail. The procedure will be scheduled at that time.

Procedure

During the procedure conscious sedation with intravenous fentanyl and Versed will be provided. Ciprofloxacin 400 mg administered intravenously prior to the procedure for antibiotic prophylaxis. The procedure will be performed in the Interventional Radiology suite by one or both of the study investigators. A Foley catheter will be placed, with the balloon filled with contrast material to assist in prostate and bladder localization. Bilateral femoral arterial access will be obtained, unless evidence of vascular disease in the iliofemoral system precludes safe bilateral access. In that event, unilateral femoral access will be obtained. Each patient will have a selective internal iliac arteriogram, and as necessary, an arteriogram of the anterior division of the internal iliac artery performed to identify the prostatic arterial supply. This typically arises from the inferior vesicle artery (also known as the prostatic artery), but may have supply from the superior vesicle, the internal pudental or obturator branches as well.

The prostatic arteries will be selected using standard micro-catheter technique. Embolization of the prostate will be performed with 300 to 500 um sized TAGM (Embosphere® Microspheres, Merit Medical, South Jordan, UT). The embolization endpoint will be absence of the normal blush of the prostate on post embolization angiography and stasis of flow in the prostate arteries.

After the catheters are removed, hemostasis will be achieved with manual compression.

Post-Procedure Care

As the primary outcome is safety, each patient will be admitted for observation and short-term recovery overnight. Analgesics will be provided via IV PCA. During the observation period, each will be assessed on the severity of pain occurring during the first 24 hours after treatment using a visual analogue scale (VAS) administered by the nurse practitioner. The assessment sheet will include a 10 cm linear VAS scale along with subjective questions regarding the patients' degree of other symptoms, specifically rectal pain or bleeding, pain with urination or gross hematuria. After discharge, the patients will be called the next day to review symptom status and to screen for complications.

Follow-up Care and Evaluation

In the Table 2 below, the baseline and follow-up visits and the associated assessments at each visit are summarized.

Table 2. Study assessment summary

Prior to treatment	Procedure	1 week after treatment	3 months	6 months	12 months and annually
IPSS and IIEF Questionnaires Medical History Physical Exam CBC, Blood Chemistry, PSA UA, Urine C&S (if indicated) Urologic exam Urine Flowmetry Cystoscopy Anoscopy MRI (if not able, TRUS)	2 hour procedure Sedation Bladder catheter (removed prior to discharge) Overnight stay Symptom assessment Adverse Event Assessment	IPSS Questionnaire Symptom Questionnaire Urologic Exam CBC, Blood Chemistry, PSA UA, Urine C&S Cystoscopy Anoscopy* Urine Flowmetry Adverse Event Assessment	IPSS and IIEF Questionnaires Urologic Exam CBC, Blood Chemistry, PSA UA, Urine C&S Urine Flowmetry Cystoscopy MRI (if not able, TRUS) Adverse Event Assessment	IPSS and IIEF Questionnaires Urologic Exam CBC, Blood Chemistry, PSA UA, Urine C&S Urine Flowmetry Cystoscopy MRI (if not able, TRUS) Adverse Event Assessment	IPSS and IIEF Questionnaires Urologic Exam CBC, Blood Chemistry, PSA (PSA only after 12 months) UA, Urine C&S Urine Flowmetry Cystoscopy (12 month only) MRI (if not able, TRUS) Adverse Event Assessment

*repeat anoscopy at subsequent visits until resolves or stable for two consecutive examinations.

Outcome Assessment Measures

Laboratory Assessment

The safety of the therapy will be monitored in part using laboratory analyses, including CBC, serum chemistry, urinalysis, urine culture and PSA. Of these, the urine testing is directed at assessing bladder function, while PSA trending will be an important outcome measure of prostate status.

Urine Flowmetry

Several tools have been developed to evaluate severity of LUTS and to track disease progression and response to therapy. Urine flowmetry, which includes voided volume (>125cc), total time of voiding, peak urine flow rate (Q_{max}), average urine flow rate, and post void urinary volume, provides an objective measure of urinary function and will be measured in this study [29].

Symptom and quality of life assessment

While urinary symptoms are increased in larger prostates, prostate size does not always predict severity of symptoms. Many patients with enlarged prostates do not have symptoms and therefore no therapy other than

watchful waiting is indicated.

To provide a means of assessing symptom severity, the AUA symptom index and International Prostate Symptom Score (IPSS) have been developed and validated and have become important clinical tools directing management of LUTS attributed to BPH [30, 31]. These are self-administered questionnaires that assess the severity of symptoms including frequency, nocturia, urgency, incomplete emptying, intermittency, straining, and a weak stream. The questionnaires only differ in that the IPSS has an added quality of life question and for this reason that will be the questionnaire we use in this study. The IPSS asks patients to quantify the severity of these symptoms on a scale from 0-5 with a total overall score ranging from 0-35. A symptom score of 0-7 is considered mild symptoms, 8-19 moderate, and 20-35 severe. The IPSS also includes a quality of life (QoL) question asking "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" with a scale ranging from 0-6 (terrible to delighted).

Erectile dysfunction is a key concern with prostate surgery and may be with prostate embolization as well. A standard questionnaire used for assessing erectile function is the International Index of Erectile Function (IIEF) [32] and a short 5 question version of this questionnaire (IIEF-5) has been developed and validated [33] and this is the version that will be used in this study.

Visual inspection of the bladder and rectal mucosa

Both cystoscopy and anoscopy will be used before and 1 week after therapy to assess the integrity of the mucosa and the impact that embolization has on the mucosa of these structures. As currently written, the cystoscopy will be repeated at 3, 6, and 12 months after therapy. Anoscopy would only be repeated if the 1 week exam is abnormal and then it will be repeated until the exam is normal or stable on 2 consecutive examinations.

Imaging Assessment

Trans rectal ultrasound is the current standard imaging for the clinical assessment of the prostate gland [29]. Having said that, MRI can provide a more comprehensive assessment of the prostate size and tissue viability. Contrast-enhanced MRI provides a perfusion "map" of the prostate and allows the determination of the extent of infarction (or non-perfusion) of the prostate. The preliminary work in both Lisbon and Sao Paulo suggests that the greater the degree of de-vascularization of the prostate, the greater the volume reduction. This is likely to correlate with symptom improvement, although this requires confirmation. We believe that this study will provide preliminary data that can be used to help design studies to test that hypothesis.

Adverse Events

Each adverse event will be recorded as they occur. Each will be categorized as to type and severity using the Society of Interventional Radiology (SIR) definitions of adverse events based on outcome. That classification is as follows:

Type	Class	Definition
Minor	A	No therapy, no consequence
	B	Nominal therapy, no consequence; includes overnight admission for observation only.
Major	C	Require therapy, minor hospitalization (<48 hours).
	D	Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours).
	E	Permanent adverse sequelae.
	F	Death.

Analysis

The primary outcome is the absence of complications to the bladder, rectum or other pelvic structures detected in the first week after therapy. Each patient will be judged free of these adverse events or not. For those with an adverse event, the complication will be scored using the SIR definitions. Descriptive statistics will be used to summarize these events, along with patient demographics and initial clinical status.

Appropriate parametric and non-parametric tests will be used to assess change in laboratory measures, urine flowmetry parameters, and scores from the IPSS and IIEF. Changes in prostate volumes and the estimated volume of devascularized tissue will be calculated for each patient and outcomes from the different embolics will be compared. Appropriate paired parametric and non-parametric tests will be used to determine statistical significance. A p value of 0.05 will be considered statistically significant.

Statistical Considerations (justification for sample size or "n", power or degree of change):
Descriptive statistics will be used to summarize these events, along with patient demographics and initial clinical status.
Appropriate parametric and non-parametric tests will be used to assess change in Q Max flow, IPSS, IIEF and the SF-36. Changes in prostate volumes and the estimated volume of devascularized tissue will be calculated.

Relative importance/value of the trial, considering "standard" therapy and competing trials:
An alternative procedure to surgery with durable results would be beneficial to patients with LUTS who cannot tolerate medical therapy or cannot have surgery performed for other comorbidities.

Feasibility of study including projections for accrual of subjects (Total and Georgetown University) and timeline for accrual:

Anticipated Accrual for local site? 30
Overall Target Accrual? 30
How Long Will Study Be Open to Accrual?_____12-24_____ month(s)
Duration of Study?____5 years after last recruited patient.

6. **Risks**: Indicate what you consider to be the risks to subjects and indicate the precautions to be taken to minimize or eliminate these risks. Justify the need for a placebo control group if one is included in this study. Where appropriate, describe the data monitoring procedures that will be employed to ensure the safety of subjects. Use additional sheets as needed.

This is a Phase I-II safety study focused on the local risks in the pelvis of this procedure. While there are other potential risks due to the iodinated contrast, arterial puncture and the passage of the catheters within the vessels, these risks are very low, well less than 5% and no greater than for any other arteriographic procedure. Other potential risks related to an embolization procedure include the risk of conscious sedation and radiation exposure. We anticipate this procedure taking on average about 30 minutes of fluoroscopy and approximately 100 angiographic images. We will use ALARA principles to reduce X-ray exposure, including tight collimation, maximizing tube subject distance, varying angulation of the X-ray beam, slow pulsed fluoroscopy rates and slow filming rates for angiographic series. We will record all available exposure factors for subsequent analysis, as well as patient BMI. The radiation safety officer at Georgetown University Hospital has reviewed our approach and has approved it from a radiation safety perspective.
We cannot accurately estimate the risk of bladder or rectal injury as detailed analysis of the currently reported patient experience has not been reported. We have visited both the group in Lisbon, who have now treated over 250 patients and the Brazilian group has treated over 70 patients. There have been no serious rectal injuries reported. There has been one injury in the Lisbon group to the bladder that resulted in the need for bladder resection.
Therefore, the current experience would suggest that the risk of complication is low, with the risk of a serious complication is extremely low (less than 1% chance) but that is based on clinical experience and not careful assessment of the rectum and bladder. This is the main focus of our study
Based on the reported data to date and known potential complications of angiographic procedures, the following are potential risks of the procedure:
Related to the embolization of the prostate: Minor or self-limited complications: burning in the urethra, urinary

infection, hematuria, hematospermia, hemorrhage, vasospasm, rectorrhagia, pain in the pelvis, or allergic reaction to embolic material.
More serious complications related to embolization of the prostate: bladder or bladder neck necrosis, possibly requiring surgical resection. Bladder ischemia causing severe pain, but resolving without complication. Other than the one case of surgical resection of the bladder in Lisbon, all reported complications have resolved with minimal or no therapy.
Complications related to angiography: arterial injury, which in rare instances (<1%) can lead to need for surgical repair of the artery, arterial injury in the pelvis, puncture site hematoma and allergic reaction to the contrast media.
Radiation injury to the skin of the buttocks- this complication is not yet reported but is possible with prolonged procedures.

Risk Minimization
As noted above, great care will be taken with the use of X-ray exposure to minimize dose. Similarly, each patient will be evaluated pre-procedure for sedation risk according to the standard of care and will be followed by both the interventional radiology and urology staff physicians.

Each significant injury to a patient's bladder or rectum will be reported immediately to the IRB staff. Those with lesser injuries will be recorded and followed to resolution. All minor and major complications will be summarized after each set of 10 patients and reported to the IRB. We currently plan to stop the study for re-evaluation of its overall safety if more than 20% of patients assessed after the first 10 patients (and each subsequent group of 10 patients) suffers either a bladder or rectal injury requiring surgical intervention.

We do not believe a data safety and monitoring committee is needed as our urology co-investigators will serve the role of safety monitors. They have a strong incentive to identify injuries, as they do not perform this procedure and it has the potential to compete with traditional therapies. While our urology colleagues are interested in providing alternatives to TURP for their patients, they have no interest in a therapy that is not safe.

7. Does a Data Safety and Monitoring Board exist?

☐ Yes ☒ No

[A Data Safety and Monitoring Board, an independent group of experts, will review the data from this research throughout the study. Patients will be told about new information from this or other studies that may affect their health, welfare, or willingness to stay in this study.]

8. Does this study include a Placebo?

☒ Yes ☐ No

9. Website Summary: If this is an open clinical trial, recruitment material for clinical trials and information for sponsors about the type of research we do will be posted on the Clinical Trials website. Please create a brief summary, in Layman Terms (8th grade language) of 200 words or less for this protocol outlining the salient features that may be useful to public and health care professionals.

http://clinicaltrials.georgetown.edu/index.html

The Departments of Radiology and Urology at Georgetown University Hospital are collaborating on a research study to determine the safety and effectiveness of prostate embolization, a new treatment for men who have enlarged prostate glands and urinary obstruction. Men with urinary obstruction usually have frequent urge to urinate, a weak urine stream, difficulty starting to urinate and may need to urinate numerous times each night.

Prostate enlargement (medically known as benign prostatic hyperplasia) is due to overgrowth of the prostate gland tissue and is very common in older men. This is not related to prostate cancer, although all patients treated in this study and for prostate enlargement in general are screened to be sure there is no evidence of prostate cancer.

The new treatment, prostate artery embolization, is a minimally-invasive procedure done while a patient is sedated. After local anesthesia, the artery at the top of the leg is entered with a catheter (a thin long tube), which is then advanced into the arteries feeding the prostate gland. Small beads are injected into the arteries to block the blood supply to the prostate tissue, causing that tissue to shrivel and shrink. The procedure takes from 2 to 3 hours and will require only an overnight observation stay in the hospital. The patient can return to normal activities within a day or two of treatment.

There are no studies on prostate artery embolization that have been completed in the United States. The studies that have been completed in other countries to date suggest that this is effective in most men in causing the urinary symptoms to significantly improve or disappear. The data so far also suggests that this is safe, with few complications.

This study will focus first on the safety of the procedure to be sure there are no injuries to other pelvic structures, such as the bladder or rectum, which are very near the prostate. The current experience in other countries suggests that these types of injuries are very rare, but we plan on a detailed analysis to accurately assess the risk. The study will also measure the severity of symptoms before and after the procedure and to evaluate whether the prostate shrinks and the extent of scarring of the prostate tissue.

With any treatment, the long-term outcome is also a key question. There are no long-term studies of this procedure yet completed. We hope to follow patients treated for up to 5 years after treatment by questionnaire to determine if once gone, the symptoms ever return.

10. Data Safety and Monitoring Plan

10.1 Assignment of Risk Levels – Please select the risk level for your study and check the boxes that apply.

10.1.A Research involving minimal risk only if one of the following applies:

☐	Anthropomorphic evaluations	☐	DEXA scans
☐	Electrocardiograms (EKGs)	☐	Exercise testing
☐	Intravenous glucose tolerance tests	☐	Intravenous catheter insertion
☐	Magnetic resonance imaging (MRI) scans	☐	Observational studies
☐	Oral glucose tolerance tests	☐	Pathology slide review
☐	Special/prescribed diets	☐	Venipuncture
☐	Other non-therapeutic tests or studies. Please list:		

Note: *In the assignment of risk levels, a research survey may be considered more than minimal risk to subjects if dealing with very sensitive information*.

10.2 Plans for Reporting of Adverse Events Including Subject's Death.

Adverse events from this protocol will need to be reported to the IRB, GCRC RSA (if the study is being conducted on the GCRC), and GCRC Nurse Manager (if the study is being conducted on the GCRC). In the section below, please list other individuals and/or entities to whom adverse events will be reported.

Individual/Entity		
☒	Investigator	
☐	National Institutes of Health and/or	
☐	Food and Drug Administration (FDA)	
☐	Other agency or sponsor	Please specify:

10.2.1 Who is the individual/entity primarily responsible for AE and to whom they are primarily reported.

Name	**Position**
James B Spies MD	Principal Investigator

Plans for Monitoring the Progress of Trials and the Safety of Participants

10.2.1 Safety tests. In the section below, please indicate the summary of safety tests, particularly those that screen out ineligible research subjects and those that monitor for toxicity and other adverse outcomes.

Clinical evaluation will be used before to exclude those that have renal insufficiency, iliac artery occlusion, and prostate cancer.

Office anoscopy and cystoscopy will be completed before the procedure and at regular intervals after to evaluate the bladder and rectal mucosa. This is the most sensitive test to detect ischemic injury.

All X-ray parameters will be recorded to estimate patient exposure. At the 1 week and 3 month office visits, each will have the skin of the buttock assessed, as this is the most likely site for an radiation injury and it should be manifest between 1 week and 3 months after exposure.

10.2.2 Safety Contact Information. In the section below, please include a description of who will manage the patients and be responsible for assessing subjects' responses including potential adverse events during their participation in the protocol. Please provide 24-hour contact information of the PI or other responsible member of the study team.

Name	**Role on the Project**	**Can be contacted 24X7?**	**Contact Information**
James B. Spies MD	Principal Investigator	Yes	Phone: 202-444-3450
			Pager: 202-405-3733
			E-mail: spiesj@gunet.georgetown.edu
Alex Kim MD	Co-Investigator	Yes	Phone: 202-444-3450
			Pager: 202-405
			E-mail: Alexander.Y.Kim@gunet.georgetown.edu
John Lynch MD	Co-investigator	Yes	Phone: 202-444-4688
			Pager: 202-405-2483
			E-mail: lynchj@gunet.georgetown.edu
Keith Kowalczyk MD	Co-investigator	Yes	Phone: 202-444-4922
			Pager: 202-4055017
			E-mail: Keith.Kowalczyk@gunet.georgetown.edu
			Phone:
			Pager:
			E-mail:

10.4.3 Description of Individuals/Entities in Charge of Dispensing Drugs. In the section below, please include the description of individuals and/or entities in charge of dispensing the drugs.

Name	**Role on the Project**	**Contact Information**
Michelle Jones, NP	Nurse Practitioner/ clinical coordinator	Phone: 202-444-5479
		Pager: 202-405-2520
		E-mail:
Merry Preziosi NP	Nurse Practitioner/clinical coordinator	Phone: 202-444-7014
		Pager: 202-405-5004
		E-mail:

10.4.4 Safety Monitoring Methods and Intervals

In the section below, please check all that apply.

Data to be Evaluated	**Interval/Frequency of Evaluation***
☐ Age specific intervention(s)	1 week after treatment, 3 months, 6 months, 12 months and annually for 5 years.
☐ Clinical test(s)	
☒ Subject interview and/or contact	
X Subject's physical exam	
☒ Subject's symptoms or performance status	
☐ Subject's vital signs	
X Other study parameters. Please list:	

10.4.5 Decision Making Criteria and Stopping Rules

In the section below, please describe data safety monitoring criteria for decision-making regarding continuation, modification, or termination of the clinical study.

The study will be stopped if any two patients in any 10 patients suffer either a bladder or rectal injury requiring surgical intervention. Thus if in the first 10 patients, two patients have this type of injury, the study will be stopped. Similarly, if two patients in any set of 10 patients has this type of injury, the study will be stopped. After each 10 patients, a report on complications will be submitted to the IRB.

10.4.6 Monitoring of the Study

In the section below, indicate who will monitor the study and to whom the study will report. Describe the frequency of the monitoring. If a DSMB is required, describe the composition of the board, its role, and the frequency of meetings and methods of communications.

The urology staff will serve as safety monitors. Each significant injury (requiring surgical intervention) to a patient's bladder or rectum will be reported immediately to the IRB staff. Lesser injuries will be recorded and followed to resolution. All minor and major complications will be summarized after each set of 10 patients and reported to the IRB.

10.4.7 Subject Withdrawals/Dropouts

In the section below, please describe how subject withdrawals/dropouts prior to study completion will be reported. Include examples of reasons that may prompt subject withdrawals/dropout.

Other than patient unwillingness to complete follow-up, we do not anticipate other reasons for withdrawals. Unless a withdrawal is associated with a significant injury, withdrawals will be reported after each 10 patients with the report regarding other complications.

Section Four: Selection of Subjects and the Informed Consent Process

11. Indicate whether this project involves any of the following subject populations?

- ☐ Children (Children are defined by local law as anyone under age 18.)
- ☐ Prisoners
- ☐ Pregnant women
- ☐ Cognitively impaired or mentally disabled subjects
- ☐ Economically or educationally disadvantaged subjects

If you indicated any of the above, in the space below please describe what additional safeguards will be in place to protect these populations from coercion or undue influence to participate. (Use additional sheets as needed.)

Not applicable

12. Recruitment: Describe how subjects will be recruited and how informed consent will be sought from subjects or from the subjects' legally authorized representative. If children are subjects, discuss whether their assent will be sought and how the permission of their parents will be obtained. Use additional sheets as needed.

Patients will be recruited via clinicaltrials.gov and also through a web page placed on the Radiology Department hospital website. The same information will be listed on both sites.

Informed consent and the HIPAA release will be obtained at the time of initial clinical assessment. The patients will all have been given the consent and patient summary prior to that visit so that they will be informed of the study procedures, the exams they will have to undergo and the anticipated risks.

13. Does the review of this protocol include evaluation of patient population to ensure women and minorities are included, if appropriate?

☐ Yes. This study is open to both men and women, and to all racial/ethnic groups. Since there are no prior reasons to expect different effects of therapy in male and female patients, and in different racial/ethnic groups, this study will not have separate accrual targets for these groups. Subgroup analyses will be conducted to determine gender and race/ethnicity treatment effects and will document any interactions between treatment and these factors.

☒ No

The study is limited to male patients with benign prostatic hypertrophy and obstructive urinary symptoms. The study is open to all racial and ethnic groups. Only patients able to read and write English will be included to facilitate completion of questionnaires.

14. Other Exclusions: Please check the corresponding box if any of the following populations is excluded.

☐ **HIV**
☐ **Pediatric**
☐ **Other** _____

Explain the rationale for excluding any sub-populations populations in the space below.

This is a male only study. Patients must be able to read and write English to complete the questionnaires.

15. Will subjects receive any compensation for participation in cash or in kind?

☐ Yes ☒ No

If subjects receive any compensation, please describe amount or kind of compensation in the space below.

Not applicable

Section Five: Privacy and Confidentiality of Data and Records

16. Will identifiable, private, or sensitive information be obtained about the subjects or other living individuals? Whether or not such information is obtained from a covered entity (GUH, WHC, etc), describe the provisions to protect the privacy of subjects and to maintain the confidentiality of data. If the information does come from a covered entity, please attach a copy of the completed appropriate HIPAA General Authorization Form or Request for Waiver. Use additional sheets as needed. HIPAA compliant forms for MedStar may be found at the following website:

http://www.medstarresearch.org/body.cfm?id=87

Each patient will be assigned a 4 digit sequential number for all patients screened for the study. Contact data will be collected but kept separate from all clinical data. A screening form will be completed by each patient, but the personal identifiers will not be included on that form. All questionnaires and all clinical data forms will be marked with the patient identification number and initials, but no other identifiers

All data forms will be kept in a locked file cabinet in a secured office. Any data entered in a computer database will be marked by the patient identification number only.

☒ I certify that the information furnished concerning the procedures to be taken for the protection of human subjects is correct. I will seek and obtain prior approval for any modification in the protocol or informed consent document and will report promptly any unexpected or otherwise significant adverse effects encountered in the course of this study.

☒ I certify that all individuals named as consultants or co-investigators have agreed to participate in this study.

☒ I assure that the protected health information identified on the "Medical Records Release and General Authorization to Use and Disclose Health Information for Research" and the persons and entities that may use, give and receive protected health information is accurate and reflective of the known use and disclosure for this human clinical study.

James B. Spies MD ____ _____ Printed/Typed Name of Investigator _____ Signature of Investigator	202-444-3450 _____ Telephone number _____ Date
Cirrelda Cooper MD _____ Printed/Typed Name _____ Signature of Department Chair	Department Chair: ☐ Approved ☐ Disapproved 202-444-3450 _____ Telephone Number _____ Date

If more than one department or administrative unit is participating in the research and/or if the facilities or support of another unit, e.g., nursing, pharmacy, or radiation therapy, are needed, then the chair or administrative official of each unit must also sign this application.

_____ Authorized Signature Chairman, Department of Urology _____ Title and Department	☐ Approved ☐ Disapproved _____ Date
_____ Authorized Signature and Title _____ Title and Department	☐ Approved ☐ Disapproved _____ Date
_____ Authorized Signature and Title _____ Title and Department	☐ Approved ☐ Disapproved _____ Date

Section Six: Attachments
Please attach the following items in order for the IRB to review your research.

24 Copies of the Following for Full Board review, only 1 copy for Expedited Review:
- ☐ IRB Application form (Form AB-1)
- ☐ Informed Consent Document
- ☐ Any recruitment notices or advertisements
- ☐ Any research survey instruments, psychological tests, interview forms, or scripts to be used
- ☐ HIPAA In-house Authorization or Request for Waiver*
- ☐ Any communications from the FDA regarding IND, IDE, or humanitarian use applications related to this submission.

One Copy of the following, when applicable
- ☐ Request for Expedited Review (Form AB-3)
- ☐ Request for Exemption (Form AB-4)

5 Copies of the Following for Full Board review, only 1 copy for Expedited Review:
- ☐ Investigator's Brochure from the sponsor, if applicable**
- ☐ Research protocol and sample consent document from the sponsor or Cooperative Group, if applicable
- ☐ For all **DOD sponsored studies – documentation of scientific review and approval**

2 Copies of the following, if applicable
- ☐ Grant application

One Copy of the following forms for Principal Investigator and **ALL** Co-Investigators
- ☐ Certificate of Completion for HIPAA training and HIPAA forms.*
- ☐ Conflict of Interest or Financial Disclosure Form
- ☐ Certificate of Completion of Education in the Protection of Human Research Subjects***
- ☐ Investigator's qualifications (CV, biosketch, or Form 1572, if available)
- ☐ If this project involves an FDA regulated drug or device, FDA form 3455

* HIPAA Training
All persons listed on the IRB application, Co-Investigators Page, Investigator's Agreement or 1572 of any research protocol will need to have completed the HIPAA training module for Researchers in order to secure IRB approval. Additionally, Investigators will need to assure that all key personnel involved in the research, especially personnel with data access and patient contact, have completed the HIPAA training module for Researchers. For more information and to download forms, please refer to the following MedStar website:
http://www.medstarresearch.org/departments/ora/HIPAA/hipaaintro.htm

** Investigator's Brochure (where applicable)
The Investigator's Brochure must contain the following information. If it does not contain the information, then please attach a separate sheet of paper to address the item.
- Name of drug under study.
- Source of the drug.
- Experience with the drug in humans, including doses tested, toxicity observed, minimal toxic dose, pharmacokinetic data (absorption, elimination, metabolism, etc.).
- Description of toxicity in humans.
- Procedures for minimizing adverse reactions and dealing with those that might occur.

*** Information on Human Subjects Protection in Research Training:
http://www.georgetown.edu/OSP/HumanSubjs.htm