Clinical Protocol Title:	EmboSphere® PROstate Post Market Study A Prospective Post Market Study of Patients with Symptomatic Benign Prostatic Hyperplasia treated by Prostatic Artery Embolization with Embosphere® Microspheres
Protocol #:	PAE-P4-17-01
Procedure:	Prostatic Artery Embolization
Device Name:	Embosphere® Microspheres
Sponsor:	Merit Medical Systems, Inc [redacted]
	[redacted]
Protocol Version:	4.0
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CONFIDENTIALITY STATEMENT

This protocol contains confidential information for use by the participating physician and designated representatives. It should be kept confidential and must be maintained in a secure location. Do not copy or distribute without written permission from the Sponsor.

INVESTIGATOR PROTOCOL SIGNATURE PAGE

STUDY TITLE:	A Prospective Post Market Study of Patients with Symptomatic Benign Prostatic Hyperplasia treated by Prostatic Artery Embolization with Embosphere® Microspheres
PROTOCOL # & VERSION:	PAE-P4-17-01 4.0
STUDY CENTER NAME & SITE NUMBER:	_____ (Print name & number of study center)

I, the undersigned, have read and understand the protocol specified above and agree with its content. I agree to perform and conduct the study as described in the protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol. I will provide copies of this protocol and all pertinent information to the Study personnel under my supervision and my hospital Institutional Review Board/Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the Merit Medical Systems investigational device and the conduct of the study according to Good Clinical Practice (GCP), Declaration of Helsinki, 21 CFR Parts 50, 54, and 56, ISO 14155:2020 and any local regulations.

_____

SITE PI – Print Name

_____

SITE PI – Signature

_____

DATE

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1 Introduction

Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in men, with more than 50% of men in their sixties and as many as 90% in their seventies and eighties having some symptoms of BPH. As life expectancy increases, so does the occurrence of BPH. In the United States in 2000, there were 4.5 million visits to physicians for BPH with a direct cost of $1.1 billion. [1-2]

Medical treatment is usually the first line therapy for lower urinary tract symptoms (LUTS) due to BPH. The two main categories of medications for management of BPH are alpha blockers and 5α -reductase inhibitors. Alpha blockers (α1-adrenergic receptor antagonists) are the most common choice for initial therapy. Patients who cannot tolerate these drugs or are refractory to treatment typically receive surgery or a minimally invasive therapy. In general, transurethral resection of the prostate (TURP) is still considered the gold standard of prostate interventions for patients who require a procedure. The procedure involves removing part of the prostate through the urethra with a resectoscope.[3-4] There are also a number of less invasive methods for reducing prostate size, including radiofrequency, microwave and laser therapies. All of these treatment methods involve introducing energy into the body and urethral access and manipulation. All these technologies have the same objective—to remove prostate tissue to relieve constriction of the urethra or bladder outlet obstruction and reduce symptoms of LUTS. They produce outcomes similar to TURP, although there is not as much data on long term effectiveness as there is for surgery. The challenge for developing new methods of treating symptomatic BPH is to reduce hyperplastic tissue and achieve good long-term control of LUTS while reducing adverse events and negative impacts on quality of life, such as ejaculatory disorders.

Embolization of prostate arteries has been used for many years to control serious bleeding after biopsy or prostatectomy. The first published case in which it was recognized that embolization could have a therapeutic effect on benign prostatic hyperplasia (BPH) was by DeMeritt and colleagues.[5] Prostate artery embolization (PAE) is an emerging therapy for LUTS associated with BPH, and has been demonstrated to reduce symptom burden, improve urodynamic measures, and decrease prostate size.[6-10] On April 16, 2013 Embosphere Microspheres received the CE mark for the indication of embolization of the prostate gland for relief of symptoms related to benign prostatic hyperplasia, and on June 21, 2017 Merit Medical Systems, Inc received 513(f)(2) (de novo) classification from the FDA to expand the indication for Embosphere Microspheres to include prostatic artery embolization (PAE) for symptomatic benign prostatic hyperplasia (BPH).

The indication was granted based on the outcomes of published and unpublished data from 286 patients. The cohort is typical of the patient population treated for symptomatic benign prostatic hyperplasia. Mean age at baseline was 67.7 ± 9.7, lower urinary tract symptoms were severe as reflected in a mean International Prostate Symptom Score (IPSS)[11] of 21.5 ± 6.8, and mean quality of life (QOL) score from the IPSS questionnaire was 4.8 ± 0.9 ("mostly dissatisfied" to "unhappy"). Bilateral prostate embolization was achieved in 254 patients (88.9%), despite including 32 patients over the age of 80 and 54 with indwelling catheters at baseline for management of acute urinary retention. Mean symptom scores improved significantly compared to pretreatment values at every follow up interval. Mean IPSS scores improved from 21.5 ± 6.8 at baseline to 6.3 ± 5.8 (<0.0001) and 6.2 ± 5.8 (<0.0001) at the 1-

3 month and 9-16-month follow-ups respectively. A reduction of IPSS score by at least 3 points was achieved at 9-16 months in 97% of patients, and 90% dropped by at least 1 symptom category.

The reduction of LUTS reflected in the IPSS changes affected mean quality of life. Mean QOL scores improved significantly from 4.8 ± 0.9 ("mostly dissatisfied" to "unhappy") pre-embolization to 1.4 ± 1.2 (<0.0001) and 1.4 ± 1.1 (<0.0001; "pleased"/ “mostly satisfied”) at the 1-3 month and 9-16-month follow-ups respectively.

2 Study Rationale

Prostatic artery embolization with Embosphere Microspheres is a relatively new procedure. The goal of this post market study is to evaluate long-term safety and effectiveness in a 'real world' setting.

3 Study Objectives

3.1 Primary Objective:

Evaluate the long-term effectiveness of prostatic artery embolization (PAE) with Embosphere Microspheres as assessed by the International Prostate Symptom Score (IPSS) for those subjects who are eligible to complete a baseline IPSS for comparative purposes.

3.2 Secondary Objectives:

- Evaluate IPSS and QoL after discontinuation of indwelling bladder catheter (IBC) post PAE
- Evaluation of device-related adverse events
- Evaluation of procedure-related adverse events
- Evaluate frequency of indwelling bladder catheter (IBC) removal post PAE
- Technical Success
    - Successful embolization of treated prostate gland
- Evaluation of additional treatments for refractory or recurrent LUTS due to BPH post PAE
- Evaluation of change from baseline in erectile function at 12 months post PAE using the Sexual Health Inventory for Men (SHIM). 12-16

3.3 Exploratory Objectives:

If sufficient data is available, additional exploratory analyses will also be conducted. These may include, but are not limited to:

- Comparison of safety and effectiveness outcomes from patients treated with Embosphere Microspheres 100-300µ vs 300-500µ
- Comparison of procedure time for patients embolized with radial vs femoral access
- Comparison of safety and effectiveness outcomes of embolizations that were/were not performed using the PErFecTED technique
- Comparison of effectiveness outcomes of bilateral vs unilateral embolizations
- Multivariate analyses to determine factors correlated to better effectiveness outcomes
- Evaluation of change from baseline prostate size at any time point post PAE

4 Study Design

This is a prospective, open label post market study to evaluate the long-term safety and effectiveness of PAE using Embosphere Microspheres. Up to 500 patients with LUTS due to BPH will be enrolled in this single arm post market study. All patients at sites who meet eligibility criteria will be offered participation. Long term effectiveness of PAE on LUTS will be evaluated by IPSS score at baseline, 3 months, 12 months, and 24 months. Note: All subjects will be asked to complete the IPSS. However, study subjects who have an indwelling bladder catheter will not be required to complete the IPSS; the IPSS questions may not be relevant to subjects with an indwelling bladder catheter. Safety will be assessed by evaluating device and procedure-related adverse events at the same time points, plus at 4 weeks following embolization. Erectile function will be assessed at baseline and 12 months by SHIM score. Additional treatments for refractory or recurrent LUTS due to BPH post prostatic artery embolization will also be recorded.

5 Eligibility Criteria

- Inclusion Criteria
  - Patient has signed informed consent
  - Patient age is 18 years or older at time of informed consent
  - Patient will undergo PAE with Embosphere Microspheres for the treatment of symptomatic BPH with LUTS
- Exclusion Criteria
  - Patient is unable or unwilling to provide follow-up information
  - Patient is undergoing PAE for reasons that do not include symptomatic BPH with LUTS
  - Any other reason the investigator deems cause for exclusion

6 Visit schedule and actions

6.1 Baseline Visit

The following baseline data will be collected:

- Date patient signs informed consent
- Demographics
- Prior BPH procedures
- Current Medication for BPH (5α-Reductase inhibitors, α-blockers, ED medications, OTC medications, etc.)

The following baseline data will be collected within 4 weeks of the study PAE procedure:

- International Prostate Symptom Score (IPSS)
  - Must be self-administered by patient
- Sexual Health Inventory for Men (SHIM)
  - Must be self-administered by patient

The following baseline data will be collected within a timeframe consistent with standard of care:

- Prostate Size Assessment
- Urinary Evaluations (Indwelling urinary catheter use, Maximum urine flow rate (Qmax), and Post void residual volume (PVR)), if done
- Prostate specific antigen (PSA), if done

The following baseline data will be collected within 12 months of the study PAE procedure:

- Prostate Biopsy, if done

6.2 Prostatic Artery Embolization (PAE) Procedure Information

The following procedural data will be collected:

- Date of procedure
- Date and time of discharge
- Embolization start and end time
- Access site (Femoral/Radial)
- Was the PErFecTED technique used? (If yes, prostate lobe(s) used on)
- Was Foley catheter with contrast used?
- Lobes embolized (Right/Left/Both)
- Size of Embosphere Microspheres
- Total Volume Administered
- Device or Procedure-related adverse events

Patients will be given a form on which to record Device or Procedure-related adverse events during the first month post procedure.

6.3 Visit 1: 4 Weeks (±1 week) Follow-Up

The following information will be collected:

- Device or Procedure-related adverse events
- Changes in indwelling urinary catheter use
- BPH related medications
- Additional prostate procedures and/or imaging
- Prostate specific antigen (PSA), if done

6.4 Visit 2, 3 &4: 3 Months (±2 weeks), 12 Months (±8 weeks), 24 Months (±8 weeks) Follow-Up

Study participation will last for a total of 24 months (± 8 weeks). Traditional visit windows are being expanded to allow for potential impacts due to COVID-19.

The following information will be collected:

- International Prostate Symptom Score (IPSS)
    - Must be self-administered by patient
- Device or Procedure-related adverse events
- Changes in indwelling urinary catheter use
- BPH related medications
- Additional prostate procedures and/or imaging

- Urinary Evaluations (Qmax and PVR), if done
- Sexual Health Inventory for Men (SHIM), 12-months only
    - Must be self-administered by patient
- Prostate specific antigen (PSA), if done

If approved by the IRB/EC, patients may receive an honorarium for complying with follow-up data collection at 12 and 24 months.

6.5 Questionnaire Administration

The International Prostate Symptom Score (IPSS) and Sexual Health Inventory for Men (SHIM) are validated for self-administration by the patient. At baseline, the IPSS and SHIM will be self-administered by the patient preferably in person during an office visit. The applicable questionnaires may also be self-administered by the patient either in person, by mail, or by email at all follow-up visits.

6.6 Additional Evaluations

Data will also be collected for additional evaluations that occur at any times outside of the above protocol-defined timepoints. If a patient receives any additional PAE procedures with Embosphere Microspheres, he will remain in the study, and the schedule for the follow-up evaluations will begin according to the date of the first PAE with Embosphere Microspheres procedure until the subject reaches a total of 24 months follow-up. End of study at 24 months is calculated on subject's first PAE procedure and not any additional PAE procedures.

Table 1. Schedule of Events

Table 1 identifies the Schedule of Events below. Follow-up may occur in the form of an in-person office visit, phone call, or mail. Information may be collected by email or text if the patient has documented that this is acceptable.

	Baseline	PAE Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled Visits
			4 Weeks (±1 week/± 7 days)	3 Months (±2 weeks/± 14 days)	12 Months (±8 weeks/±56 days)	24 Months (±8 weeks/ ±56 days)	
Informed Consent	X						
Demographics	X						
Prostate Size Assessment	X[4]						
Prior BPH Procedures	X						
Prostate Biopsy	X[1]						X[5]
Prostate Specific Antigen (PSA)	X[4]		X		X		X[5]
PAE Procedure		X					
Sexual Health Inventory for Men (SHIM)	X[2]				X		
International Prostate Symptom Score (IPSS)	X[3]			X	X	X	X[5]

	Baseline	PAE Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Unscheduled Visits
			4 Weeks (±1 week/± 7 days)	3 Months (±2 weeks/± 14 days)	12 Months (±8 weeks/±56 days)	24 Months (±8 weeks/ ±56 days)	
BPH related medications (5α-Reductase inhibitors, α-blockers, etc.)	X		X	X	X	X	X[5]
Device or Procedure-Related Adverse Events		X	X	X	X	X	X[5]
Urinary Evaluations (Indwelling urinary catheter use, Qmax and PVR)	X[4]			X	X	X	X[5]
Additional prostate procedures and/or imaging			X	X	X	X	X[5]

[1] Prostate biopsy within 12 months of PAE procedure

[2] Baseline SHIM to occur within 4 weeks of PAE procedure

[3] Baseline IPSS to occur within 4 weeks of PAE procedure

[4] Within timeframe consistent with standard of care

[5] Unscheduled visits may include one or more of the identified evaluations

7 Patient Completion and Discontinuation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any reason. If a patient is withdrawn or discontinued from the study, the reason for withdrawal from the study will be recorded on the end of study form. These subjects will not be replaced.

A subject will be considered lost to follow-up if he fails to return for more than one scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit within the allowable visit timeline and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study
- Before a subject is deemed lost to follow-up, the Investigator(s) or designees will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts must be documented

- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

If a patient receives any non-PAE BPH procedure other than biopsy after his study PAE he will be automatically discontinued from the study, and follow-up data will no longer be collected. BPH procedures that will automatically discontinue the patient include but are not limited to TURP, Urolift, microwave ablation, aquablation, laser therapy and non-Embosphere Microspheres PAE.

Patients requiring multiple PAE procedures:

- If a patient receives an additional PAE procedure with Embosphere Microspheres after the initial treatment, he will remain in the study, and the schedule for the follow-up evaluations will begin according to the date of the first PAE with Embosphere Microspheres procedure until the subject reaches a total of 24 months follow-up. End of study will be calculated based on first PAE procedure for 24 months.
- If a patient receives more than one PAE procedure to complete the initial treatment, he will remain in the study, and the schedule of the follow-up evaluations will begin according to the date of the first PAE with Embosphere Microspheres, but not to exceed a total of 24 months from initial treatment date.

8 Statistical Considerations

8.1 Endpoint Definitions

8.1.1 Primary Endpoints

The primary endpoint is the IPSS at 12 months.

8.1.2 Secondary Endpoints

The following are the secondary endpoints:

- IPSS measured at 3, 12, and 24 months post-baseline
- Device or Procedure-Related Adverse event rate at post-procedure, 3, 12, and 24 months
- Technical Success defined as the successful embolization of the treated prostate gland
- Frequency of indwelling bladder catheter removal post PAE at 3, 12, and 24 months
- Number of patients and types of treatment for refractory or recurrent LUTS due to BPH post PAE at 3, 12, and 24 months
- Change form baseline in Sexual Health Inventory for Men (SHIM) at 12 months post-PAE.

8.1.3 Exploratory Endpoints

During unscheduled visits, depending on the site's standard or care, the following measurement may be collected during the visit:

- Maximum Urinary Flow Rate (Qmax)

- Pulse Volume Recording
- Prostate-Specific Antigen
- Prostate size assessment
- Prostate biopsy

8.2 Primary Statistical Objective

The primary statistical objective is to evaluate the efficacy of the device by estimating the change from baseline in the 12 month IPSS within +/- 1 unit.

8.3 Sample Size

The sample size is based on the following assumptions

- Four countries with asymmetrical countrywide enrollments ranging from 15% to 25% of the total enrollment (conservative assumption)
- Standard Deviation = 8.5
- Difference between the lower and upper 2-sided 95% Confidence interval = 2
- 10% of patients missing either baseline or 12 month IPSS

A sample size of up to 500 patients is required to estimate the 12 month change from baseline in the IPSS within +/- 1 unit. Sample size calculations were performed using NCSS PASS 2020's procedure for one mean in a stratified design.

8.4 Analysis Populations

8.4.1 Full Analysis Set (FAS)

Includes all patients that were enrolled except those that withdrew consent before the index procedure. The FAS is the population that will be used in determining endpoints except for efficacy endpoints

8.4.2 Evaluable Analysis Set (EAS)

Includes FAS patients where there are no significant deviations (e.g. not meeting the inclusion/exclusion criteria) from the protocol that did not have an indwelling catheter at the end of the procedure.

8.5 Statistical Analyses

8.5.1 General Approach

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analyses will be conducted using {SAS version 9.4 or later (SAS Institute Inc., Cary, NC)} or other widely accepted statistical or graphical software as required.

8.5.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may

be presented, where appropriate, using the t-distribution for continuous data and exact binomial method for categorical variables.

8.5.1.2 Timing

Overall Timing: Day 0 is the date of the procedure. Study Day will be calculated relative to the randomization as follows:

- Study Day = Assessment Date – Procedure Date

Duration: Duration variables will be calculated as follows:

- Duration Days = Start Date – End Date

A day is defined as 24 hours, from 0:00 to 23:59. 24:00 means 0:00 of the next day.

Each subject duration in the study will be based on the last study contact date, which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit, including date of death.

Visit Windows: Unless otherwise specified, visit assessments will be analyzed for each analysis time point according to the study visit entered in the electronic Case Report Form (eCRF) to determine if the visit was within compliance.

8.5.1.3 Statistical Significance

Unless otherwise specified, statistical testing will be performed at the two-sided 0.05 significance level unadjusted for multiple testing. P-values will be rounded to three decimal places. If a p-value is less than 0.001, it will be reported as "<0.001". If a p-value is greater than 0.999, it will be reported as ">0.999".

8.5.1.4 Reporting Precision

Unless otherwise specified, the following conventions will apply for data displayed. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places. For continuous parameters, means and medians will be reported to 1 additional decimal place than the measured value. In contrast, the standard deviation will be reported to 2 additional decimal places than the measured value. Minimum and maximum values will be reported to the same precision as the measured value.

8.5.1.5 Missing Data

All attempts will be made to limit the amount of missing data. For all analyses of the primary endpoints, the number of observations available will be reported so the reader can assess the impact of missing data. For all clinical endpoints except for the patient-reported outcome measurements, an adjustment to the denominator will be made based on the amount of evaluable data. For each visit (or reporting time point), the event rate will be calculated as the number of subjects with certain event terms over the number of evaluable subjects. The evaluable subjects at each reporting time point include all subjects who are enrolled and

1) had an event within (on or before) the reporting cutoff days, or

2) had a follow-up at or after the lower limit of the reporting window, or
3) the withdrawal consent date/recorded lost-to-follow-up date at or after the lower limit of the reporting window.

8.5.1.6 Adverse Event Dates

More generally, in the case of partial adverse event onset date or date of death, the unknown portion of the date of the event will be imputed. If the month and year are known, the 15th of the month will be used for analysis. If only the year is known, the event will be analyzed as if it occurred on June 30th of the known year. In the rare case that the date is fully unknown, the date will be imputed as the initial treatment date. Imputation of partial dates is subject to the condition that it must occur on or after the initial treatment date. In the case where the imputed date is before the initial treatment date, the date of the initial treatment will be used. As death cannot occur before any documented subject contact, for date of death, the imputed date of death must occur on or after the last known contact in the study.

8.5.1.7 Analytical Methods

Time-dependent response variables will be expressed using the Kaplan-Meier curve, and the hazard ratio and the 95% confidence limit will be reported. Data for all categorical endpoints (e.g., TLF rate at a specific time point, etc.) are shown with the number of patients, percentage, and Clopper-Pearson's exact 95% confidence interval. Differences between treatment groups are shown using a 95% confidence interval of the difference. Analyses of secondary endpoints are conducted with the FAS population.

8.5.2 Analysis of the Primary Endpoint

The stratified sample mean change from baseline in 12 month IPSS is estimated as follows.

$$\bar{x} = \sum_{h=1}^{L} \frac{N_h}{N} \sum_{i=1}^{n_h} \frac{X_{hi}}{n_h} = \sum_{h=1}^{L} \frac{N_h}{N} \bar{x}_h$$

where $\bar{x}$ is the stratified sample mean, L is the number of strata, X_{hi} is change from baseline in 12 month IPSS for the i^{th} patient in the h^{th} stratum, N is the overall sample size and N_h. is the sample size in stratum h

It can be shown in T. Yahane(1967) that the expected value and variance of $\bar{x}$ (V($\bar{x}$)) assuming sampling without replacement are

$$E(\bar{x}) = u$$

$$V(\bar{x}) = \sum_{h=1}^{L} \left(\frac{N_h}{N}\right)^2 \left(\frac{N_h - n_n}{N_h n_h}\right) S_h^2$$

$$S_h^2 = \frac{1}{N_h - 1}\sum_{i=1}^{N_h}(X_{hi} - \mu_h)^2$$

where

The 95% confidence interval (*CI(μ)*)s calculated as follows:

$$CI(\mu) = \bar{x} \pm z_{1-\alpha/2}\sqrt{\hat{V}(\bar{x})}$$

where α is the type I error and $\hat{V}(\bar{x})$ is the unbiased estimator of $V(\bar{x})$ and is calculated as follows:

$$\hat{V}(\bar{x}) = \sum_{h=1}^{L}\left(\frac{N_h}{N}\right)^2\left(\frac{N_h - n_n}{N_h n_h}\right)s_h^2$$

$$s_h^2 = \frac{1}{n_h - 1}\sum_{i=1}^{n_h}(X_{hi} - \bar{x}_h)^2$$

.

8.5.2.1 Missing Data

Missing data for the IPSS will be imputed as the age-specific average for that time point. Also, a tipping point analysis will be performed where the analysis will be performed, excluding the missing data. The number of missing data points it takes to tip the results from one direction to the other will be reported.

8.5.2.2 Multivariate Model

A multivariate linear model will be developed to describe the IPSS changes over time. Univariate analysis will be performed analyses for all the baseline characteristics. Based on those results combined with clinical judgment, a final set of baseline characteristics will be created for use in the multivariate model. LASSO (least absolute shrinkage and selection operator; also Lasso or LASSO) regression analysis method will be used to perform variable selection and regularization to minimize the unexplained variability and enhance the interpretability of the statistical model it produces.[1]

8.5.3 Analysis of the Secondary Endpoints

8.5.3.1 IPSS changes over time

The changes over time in the IPSS using the EAS will be modeled using a linear mixed model where country and patient will be considered a random effect. If there is evidence of non-linearity, a nonlinear mixed-effects model using a 3rd-degree

[1] Tibshirani, Robert (1996). "Regression Shrinkage and Selection via the lasso". Journal of the Royal Statistical Society. Series B (methodological). Wiley. 58 (1): 267–88. JSTOR 2346178.

polynomial will be implemented. The predicted curve and 95% confidence interval will be reported. Missing data will not be imputed.

Sensitivity analyses using complete cases and missing values replaced with an age-specific average will be performed.

A multivariate linear model will be developed to predict the IPSS changes over time. Univariate analysis will be performed analyses for all the baseline characteristics. Based on those results combined with clinical judgment, a final set of baseline characteristics will be created for use in the multivariate model. The LASSO regression analysis method will be used to perform variable selection and regularization.

8.5.3.2 Device or Procedure-Related Adverse event rate at post-procedure, 3, 12, and 24 months

Treatment-related adverse event rates will be discussed in section 9.3.

8.5.3.3 Technical Success

Technical success will be reported separately as the proportion and the 95% confidence interval of patients in FAS that achieve technical success.

8.5.3.4 Successful embolization

For each of the following, the proportion and the 95% confidence interval of patients in FAS will be reported:

- Successful embolization of the right prostate gland during the index procedure
- Successful embolization of the left prostate gland during the index procedure
- Successful embolization of both left and right prostate glands during the index procedure

8.5.3.5 Number of patients and types of treatment for refractory or recurrent LUTS due to BPH post-PAE

The types of treatment and the number of patients that received that treatment for refractory or recurrent LUTS due to BPH post-PAE will be reported at 3, 12, and 24 months, and overall will be reported using the FAS.

8.5.3.6 Sexual Health Inventory for Men over time

The mean and 95% confidence interval of the change from baseline in the Sexual Health Inventory for Men (SHIM) will be reported using the EAS at 12 months post-PAE.

8.5.3.7 Removal of In-dwelling catheter

Using the FAS, for patients who had an indwelling catheter during the procedure, the proportion of indwelling bladder catheter (IBC) removal post-PAE will be reported at 3 and 12 months PAE.

8.5.4 Safety Analyses

All device or procedure related adverse events (AEs) collected will be summarized cumulatively throughout the follow-up time. The frequency count of AEs and the unique number of subjects who had the AEs will be presented. Also, the frequency and percentage of patients who had a Serious AE (SAE), or a treatment-related serious AE will be tabulated separately. If a patient experienced multiple AEs, only the most severe event or the most intense relationship to the study device would be counted within an AE code. The following information will be reported about each AE; start date, stop date, severity, relationship, expectedness, outcome, and duration.

The time-sensitive nature of any response variable may be displayed by using a Kaplan-Meier plot.

8.5.5 Baseline Descriptive Statistics

A table of clinically relevant baseline variables will be created using the methods described in section 8.5.1.1.

8.5.6 Planned Interim Analyses

There are no planned interim analyses. Results will be reported after all the patients reach the primary endpoint and then at 24 months.

8.5.7 Subgroup Analyses

The following subgroups will be evaluated for the primary and secondary endpoints:

- Patients treated with Embosphere Microspheres 100-300µ vs. 300-500µ
- Comparison of procedure time for patients embolized with radial vs. femoral access
- Embolizations that were/were not performed using the PErFecTED technique
- Bilateral vs. unilateral embolizations

8.5.7.1 Exploratory analyses

Descriptive statistics may be generated for the exploratory endpoints. Additional analyses may be performed based on the data collected. However, any analyses performed using the exploratory endpoint will be hypothesis-generating, and no conclusions will be drawn from the results of these analyses.

[redacted]

9 Device or Procedure-Related Adverse Events

A Device or Procedure-related adverse event is defined in this post market study as any event that began on or after the date of the PAE procedure and is considered related to the study procedure and/or device by the investigator. All related events must be reported in the case report form and followed until resolution.

9.1 Severity of an Adverse Event

The Investigator, based on his/her clinical judgment and the following definitions, must rate severity of the adverse event:

- Mild; Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would generally not require medication or a medical evaluation; signs or symptoms are transient (e.g., headache treated with acetaminophen, common cold, etc. would be considered mild).
- Moderate; Interferes with the subject's usual activity and/or requires symptomatic treatment.
- Severe; Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

9.2 Relationship of Adverse Event to Device and/or Procedure

The Investigator, based on his/her clinical judgment and the following definitions, must determine the relationship of the adverse event to the device and/or procedure:

- Possible: The AE/SAE follows a reasonable temporal sequence from the time of study procedure, and/or follows a known response pattern to the study procedure but could have been produced by other factors.
- Probable: The AE/SAE follows a reasonable temporal sequence from the time of study procedure, follows a known response pattern to the study procedure, and cannot reasonably have been produced by other factors.
- Definite: The AE/SAE follows a reasonable temporal sequence from the time of study procedure; follows a known response pattern to the study procedure; and cannot have been produced by other factors.

9.3 Device or Procedure-Related Serious Adverse Events

A device or procedure-related serious adverse event is defined in this post market study as any event that began on or after the date of the PAE procedure and is considered related to the study procedure and/or device by the investigator. A device or procedure-related adverse event will be considered serious if it meets one of the following criteria:

- Results in death
- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned)
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions

9.4 Reporting of Serious Adverse Events

Any treatment-related SAE that occurs on or after the date of the PAE or worsened in severity or frequency after the PAE must be reported to the Sponsor immediately (not to exceed 24 hours within site notification of the event) in the case report form or via email. It is the responsibility of Investigators to inform their IRB/EC of complications or serious injury as required by their IRB/EC procedure and/or federal law. Merit Medical is responsible for relaying information about serious adverse events and/or treatment related adverse events to the other participating Investigators and regulatory bodies as required.

10 Data Recording and Retention

The sponsor will provide each site with access to an electronic CRF for study data recording. All trial documents must be retained for a minimum of two years after the completion of the post market study or longer per the Sponsor's request.

11 Publication Policy

The Sponsor intends to publish the clinical results of this investigation and the terms are delineated in the Investigator/Site Clinical Trial Agreement. In addition, Sponsor will list this post market study on clinicaltrials.gov.

12 Good Clinical Practice (GCP)

The study will be conducted in accordance with the International Conference on Harmonization (ICH) E6 for Good Clinical Practice (GCP). The investigators will be thoroughly familiar with the appropriate use of the treatment procedure as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the trial, and retained according to the appropriate regulations.

13 Ethical Considerations

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

14 Patient Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his guardian or legal representative prior to any study procedures. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

Patients who wish to provide information for follow-up visits or receive reminders by email or text must sign a consent for this to be done over unsecured media.

15 Subject Enrollment

All patients requiring an intervention due to reasons detailed in this protocol are potential study candidates and shall be screened for eligibility. Subjects who are consented and meet all the study inclusion criteria and none of the study exclusion criteria and are treated or attempted to be treated will be considered enrolled into the study.

16 Patient Confidentiality

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

17 Monitoring, Audit and Inspection

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

18 Safety Medical Monitor

An independent safety medical monitor shall be responsible for systemic review and adjudication of specified events (e.g., all treatment-related adverse events and all deaths) . At a minimum, assess the reported event with the associated documented risks of device, vascular embolization, and PAE treatment.

Potential risk for Embosphere Microspheres:

- Immune reaction in patients who are hypersensitive to collagen or gelatin (careful consideration should be given prior to using this product in patients who are suspected to be allergic to injections containing gelatin stabilizers)

Potential risk for vascular embolization:

- Paralysis resulting from untargeted embolization or ischemic injury from adjacent tissue edema
- Undesirable reflux or passage of Embosphere Microspheres into normal arteries adjacent to the targeted lesion or through the lesion into other arteries or arterial beds, such as the internal carotid artery, pulmonary, or coronary circulations
- Pulmonary embolism
- Ischemia at an undesirable location, including ischemic stroke, ischemic infarction (including myocardial infarction), and tissue necrosis
- Capillary bed occlusion and tissue damage
- Vessel or lesion rupture and hemorrhage
- Vasospasm
- Recanalization
- Foreign body reactions necessitating medical intervention
- Infection
- Complications related to catheterization (e.g., hematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgment, and nerve and/or circulatory injuries, which may result in leg injury)
- Allergic reaction to medications (e.g., analgesics)
- Allergic reaction o contrast media or embolic material
- Pain and/or rash, possibly delayed form the time of embolization
- Death
- Blindness, hearing loss, loss of smell, and/or paralysis

PAE specific potential complications:

- Non-targeted embolization of the rectum, bladder, scrotum, penis, or other areas
- The most frequent post-procedure complication includes "Post-PAE Syndrome," which includes nausea, vomiting, fever, pelvic pain, burning sensation, dysuria, and frequent or urgent urination
- Skin burn (radiation exposure) form prolonged fluoroscopy time
- Blood in urine, semen, or stool
- Bladder spasm
- Hematoma at the catheter site
- Urinary tract infection
- Urinary retention
- Constipation

The safety medical monitor will be an independent physician with experience in interventional peripheral endovascular procedures for prostate artery embolization. In order to enhance objectivity and reduce the potential for bias, the safety medical monitor shall be independent of the Sponsor as well as the investigational sites and investigators. The methodology for performing these responsibilities shall be developed and outlined in the safety monitoring charter. Operational provisions shall be established to minimize potential bias.

19 References

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