EVEREST-I

Evaluation of Optilume™ BPH Prostatic Drug Coated Balloon Dilation Catheter in the Treatment of Moderate-to-Severe Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia

PROTOCOL No. PR1051

REVISION No. 4.0

March 25, 2022

SPONSOR

Urotronic Inc

2495 Xenium Lane N

Minneapolis, MN 55441

USA

This study will be conducted in compliance with the protocol and applicable regulatory requirements.

UROTRONIC

EVEREST-I

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I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital Ethics Committee/Research Ethics Board (EC/REB). I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to this protocol, applicable regulatory requirements, and hospital EC/REB requirements.

I agree to and understand the material presented in this protocol and must not publicly disclose in any manner the design, results, or conclusions of this investigation without prior written consent from Urotronic.

_____

Clinical Site Name

_____ _____

Site Investigator Signature Date

_____

Site Investigator, Printed Name

Protocol Summary

Title:	EVEREST-I: Evaluation of Optilume™ BPH Prostatic Drug Coated Balloon Dilation Catheter in the Treatment of Moderate-to-Severe Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia
Investigational Device:	Optilume™ BPH Prostatic Drug Coated Balloon Dilation Catheter System
Objective:	To evaluate the safety and efficacy of Optilume™ BPH Prostatic Drug Coated Balloon (DCB) Dilation Catheter System in the treatment of benign prostatic hyperplasia (BPH). 1. To assess the efficacy of the Optilume BPH Prostatic DCB Dilation Catheter System to alleviate lower urinary tract symptoms (LUTS) believed to be secondary to BPH (LUTS/BPH). 2. To evaluate the safety of the Optilume BPH Prostatic DCB Dilation Catheter System in the treatment of LUTS/BPH.
Study Design:	Prospective, multi-center, open-label, non-randomized global study
[redacted]	[redacted]
[redacted]	[redacted]
Endpoints	Primary Efficacy Endpoint: Change in IPSS score at 3 months A therapeutic responder is defined as a subject who has an IPSS improvement of $\geq$ 40%. The study is considered a success if at least 50% of the subjects are considered responders. Primary Safety Endpoint: Major Device or Procedure Related Complications at 3 Months Any of the following major device or procedure related complications at 3 months: • Device or procedure related new onset severe urinary retention lasting > 14 consecutive days post-healing

	• Device or procedure related unresolved new onset stress urinary incontinence by 90 days • Device or procedure related bleeding requiring transfusion Secondary Endpoint 1: Average Improvement of IPSS Compared to Baseline at each of the major follow up timepoints at or after 3 months Secondary Endpoint 2: Change in Peak urinary flow rate (Qmax) Secondary Endpoint 3: Proportion of subjects whose IPSS improvement is $\geq$ 30%, 40%, 50% and 75% post-treatment at each of the major follow up timepoints at or after 3 months
	Exploratory Endpoints: E1: Change in pain score E2: Change in IIEF (International Index of Erectile Function) E3: Change in EQ-5D quality of life E4: Subject satisfaction E5: Procedure parameters E6: Change in MSHQ-EjD
Inclusion Criteria:	1. Male subject > 50 years of age who has moderate-to-severe LUTS (IPSS score of $\geq$ 13) and is a candidate for interventional therapy 2. LUTS felt to be secondary to an enlarged prostate (henceforth termed LUTS/BPH) 3. Peak urinary flow rate (Qmax) $\geq$ 5 mL/sec and $\leq$ 15 ml/sec with minimum voided volume of $\geq$ 125 ml 4. Post-void residual (PVR) $\leq$ 250 ml 5. Prostate volume 20 - 80 gm as determined by TRUS 6. Prostatic urethra length is 35 – 55 mm as determined by TRUS 7. Able to complete the study protocol in the opinion of the investigator
Exclusion Criteria:	1. Interested in maintaining fertility and unwilling to use protected sex for the first 30 days post treatment 2. Unwilling to abstain or use protected sex for ninety (90) days post treatment if sexual partner is of child bearing potential 3. Presence of a penile implant or stent(s) in the urethra or prostate 4. Any prior minimally invasive intervention (e.g. TUNA, Balloon, Microwave, Rezūm, UroLift) or surgical intervention of the prostate

	5. PSA > 10 ng/ml unless prostate cancer is ruled out by biopsy. If PSA is > 4 ng/ml and ≤ 10 ng/ml, prostate cancer must be ruled out to the satisfaction of the investigator via additional tests including digital rectal exam (DRE) and/or biopsy 6. Confirmed or suspected malignancy of prostate or bladder 7. Active or history of epididymitis within the past 3 months 8. Previous pelvic irradiation or radical pelvic surgery 9. Documented active urinary tract infection (UTI) by culture or bacterial prostatitis within last year documented by culture (UTI is defined as >100,000 colonies per ml urine from midstream clean catch or catheterization specimen) 10. Visible hematuria with subject urine sample without known contributing factor 11. Neurogenic bladder or sphincter abnormalities or neurological disorders that might affect bladder or sphincter function 12. Previous or current diagnosis of urethral strictures, bladder neck contracture or detrusor muscle spasms 13. Use of beta blockers, antihistamines, anticonvulsants, or antispasmodics within 1 week prior to treatment unless there is documented evidence of stable dosing for last 6 months (no dose changes) 14. Use of alpha blockers, antidepressants, anticholinergics, androgens, daily tadalafil or gonadotropin-releasing hormonal analogs (prescribed for BPH) within 3 weeks prior to treatment 15. Use of 5-alpha reductase inhibitor within 6 months prior to treatment 16. Incidence of spontaneous urinary retention within 6 months prior to baseline assessment 17. Post-void residual volume > 250 ml or catheter dependent bladder drainage 18. Overactive bladder (OAB) or urge incontinence 19. Known poor detrusor muscle function (e.g. Qmax < 5 ml/sec) 20. Current bladder stones or prostatic calculi 21. Biopsy of prostate within 30 days prior to procedure or planned within 30 days following the procedure 22. History of cancer in non-genitourinary system which is not considered cured (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered cured if there has been no evidence of cancer within five years 23. History of clinically significant comorbidities or presence of unstable conditions (e.g. cardiovascular, lung, renal [serum creatinine > 2.0 mg/dl], hepatic, bleeding disorders, or metabolic impairment) that may confound the results of the study or have a risk to subject per investigator's opinion

	24. Any cognitive disorder that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affects the ability to complete the study quality of life questionnaires 25. Expected life expectancy < one year 26. Unable or unwilling to sign the Informed Consent Form (ICF) and/or comply with all the follow-up requirements 27. Currently enrolled in or plan to enroll in another investigational clinical trial for any disease except for observational only study 28. In the opinion of the investigator, it is not in the subject's best interest to participate in the study 29. Current treatment with anti-coagulants (e.g., warfarin or enoxaparin) or anti-platelet medications other than aspirin (e.g., clopidogrel) 30. Anatomy, e.g. presence of false passage or size of meatus, is not suitable for treatment in this study 31. Device that corresponds with the subject’s prostate size per the IFU is not available 32. Intravesical prostatic protrusion (IPP) > 1 cm 33. Current uncontrolled diabetes (hemoglobin A1c > 7%) 34. Unable or unwilling to provide all the protocol-required semen samples 35. Sensitivity to paclitaxel, on medication that may have negative interaction with paclitaxel, or contraindicated for systemic paclitaxel

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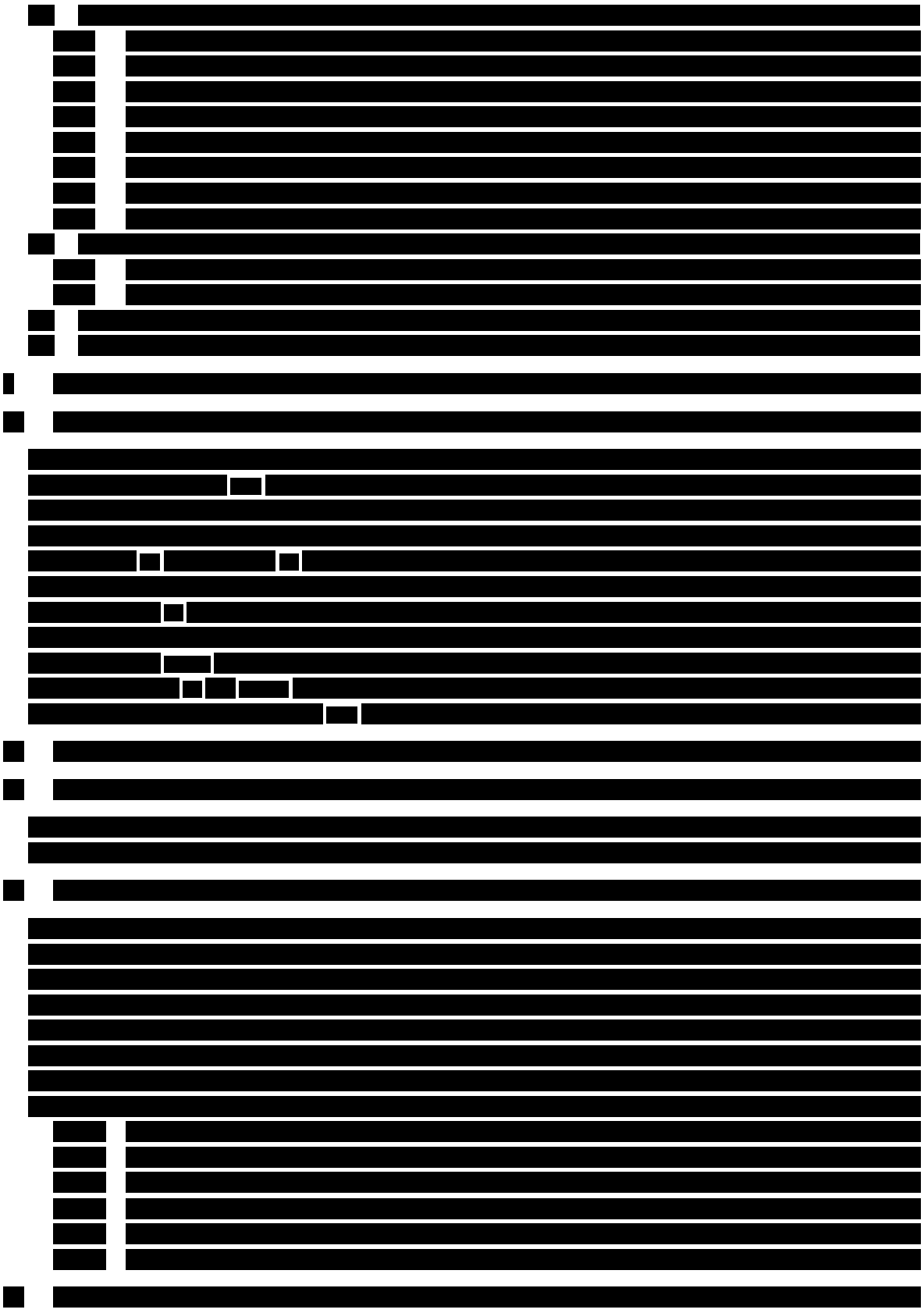

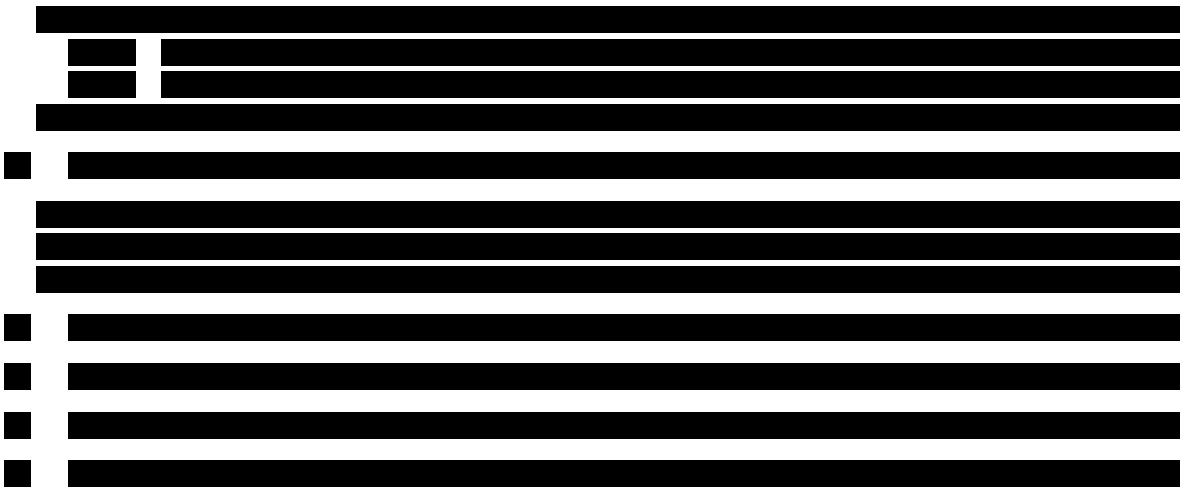

List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
AUASI	American Urological Association Symptom Index
BPH	Benign Prostatic Hyperplasia; also known as Benign Prostatic Hypertrophy
BPHII	BPH Impact Index (bother Score)
BUN	Blood Urea Nitrogen
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCB	Drug Coated Balloon
EC/REB	Ethics Committee/Research Ethics Board
EQ-5D	Standardized instrument for use as a measure of health outcome
GCP	Good Clinical Practices
ICF	Informed Consent Form
IFU	Instructions for Use
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
LUTS	Lower Urinary Tract Symptoms
LUTS/BPH	LUTS Secondary to BPH
MedDRA	Medical Dictionary for Regulatory Activities
MSHQ-EjD	Male Sexual Health Questionnaire to assess ejaculatory dysfunction
PI	Principal Investigator
PK	Pharmacokinetics
PSA	Prostate Specific Antigen
PV	Prostate Volume
PVR	Post Void Residual Urine Volume
Qmax	Peak Flow Rate
QoL	Quality of Life
SAE	Serious Adverse Event
TRUS	Transrectal Ultrasonography
TUMT	Transurethral Microwave Thermotherapy
TUNA	Transurethral Needle Ablation
TURP	Transurethral Resection of the Prostate
UADE	Unanticipated Adverse Device Effect
UTI	Urinary Tract Infection

1 INTRODUCTION

1.1 Disease State Overview and Epidemiology

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.[1,2] BPH with associated lower urinary tract symptoms (LUTS) is a common medical condition in the aging male. The prevalence and the severity of LUTS in the aging male can be progressive, and is an important diagnosis in the healthcare of our patients and the welfare of society. BPH is the second highest reason for patients to seek a urologist.[3] The incidence has been estimated to increase from 40% among males between the ages of 50 and 60 years to 90% among males older than 80 years of age.[4] In 2015, there were 38.1 million men with BPH pathology and 21.3 million with International Prostate Symptom Score (IPSS) >7; 12.2 million of them were managed for LUTS secondary to BPH (LUTS/BPH), primarily with watchful waiting (35%) and drug management (54.8%).[3]

Initially, watchful waiting (observing without treatment) is normally employed. Treatment initiation usually occurs once symptoms of bladder outlet obstruction and bladder irritability interfere with the patient's quality of life. The American Urological Association Symptom Index (AUASI) and the IPSS are now considered the gold standard measurement tools for the assessment of LUTS and response to treatment.

Medications are the most common way to control mild to moderate symptoms of BPH and significantly reduce major symptoms for many men who try them. However, medications have systemic side effects, are costly in the long run, and some patients may have difficulty with complying with the medication, particularly in the older population. Further, many patients have moderate to severe symptoms that are not fully alleviated by medical therapy.

Transurethral surgical resection of the enlarged prostate (TURP) is still considered a bench mark for the treatment of moderate-to-severe LUTS/BPH or other BPH-related complications.[5] However, surgical intervention, by definition, is the most invasive option for BPH management.

For this reason, minimally invasive therapies have been gaining favor over medication and over the traditional TURP even though the effectiveness of minimally invasive procedures has been reported to be less than TURP. Development of an effective treatment method but one with shorter treatment time, fewer complications, and faster recovery time, would be an advantage.

1.2 History of Use of Paclitaxel

Paclitaxel has been used extensively and successfully in drug-coated devices to reduce the rate of stenosis in vascular tissue. Examples of the devices coated with this drug and the dates of approval in the US are shown in Table 1. The improvement in restenosis rates led Urotronic to design a similar system to treat urinary strictures and obstructive BPH.

Table 1: US Approved Paclitaxel Coated Devices

Drug Coated Balloon	US Approval Date
Boston Taxus DES	2004
Cook Zilver PTX DES	2012
Lutonix DCB	2014
Medtronic DCB	2015
Covidien/Spectranetics/Philips Medical Stellarex DCB	2017

1.3 Previous Clinical Experiences on DCB in the Treatment in Urethra

Optilume™ Urethral Drug Coated Balloon (DCB) Catheter is currently under investigation for urethral stricture. To date 57 subjects have been treated with the Optilume Urethral DCB Catheter with promising results with no serious device-related complications. The amount of drug found in the blood system and semen is negligible. Drug is limited mostly to the treated site within the first 30 days.

1.4 Rationale for Study

Balloon dilation is one of the least invasive interventional therapies to treat BPH. Extensive clinical research on balloon dilation of the prostate was completed in the 1990s using balloon sizes ranging from 20-35mm. These studies showed that balloon dilation was safe (no adverse events reported in any study) and well tolerated by patients. However, mixed efficacy at 3-6 months in certain patient populations and 12-month LUTS reoccurrence for many patients caused the technology to be abandoned.

Urotronic's Optilume™ BPH Prostatic Drug Coated Balloon Dilation Catheter System combines the procedural advantage and short-term efficacy of balloon dilation with a localized delivery of paclitaxel to prevent future cellular proliferation and scar tissue generation during the healing process. The goal of this technology is to provide immediate relief via balloon dilation and create lasting durable results to alleviate the Lower Urinary Tract Symptoms (LUTS) associated with BPH.

This study is designed to determine the initial safety and efficacy of the Optilume BPH Prostatic Drug Coated Balloon (DCB) Dilation Catheter System to alleviate moderate-to-severe LUTS/BPH.

2 DEVICE DESCRIPTION

The Optilume™ BPH Prostatic Drug Coated Balloon Dilation Catheter System consists of two investigational catheters, a pre-dilation balloon used to initially expand the prostate, as well as the drug coated balloon which further dilates and delivers drug to the prostate. The pre-dilation balloon is constructed identically to the drug coated device, but without the paclitaxel drug coating. The pre-dilation and drug coated balloon catheters will be packaged separately.

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The device is intended for single use and provided sterile packaged within a Tyvek pouch. The pouch is sealed within a foil pouch with a desiccant within the foil pouch.

The full device description and balloon sizes available for the study are described in the Instructions for Use.

3 STUDY OBJECTIVES AND DESIGN

3.1 Objective

The objective of the study is to evaluate the safety and efficacy of the Optilume™ BPH Prostatic Drug Coated Balloon Dilation Catheter System in the treatment of BPH.

- To assess the efficacy of the Optilume BPH Prostatic DCB Dilation Catheter System to alleviate LUTS believed to be secondary to BPH (LUTS/BPH)
- To evaluate the safety of the Optilume BPH Prostatic DCB Dilation Catheter System in the treatment of LUTS/BPH

3.2 Study Design

This is a prospective, non-randomized, open label, multi-center study. [redacted]

3.3 Study Endpoints

3.3.1 Primary Efficacy Endpoint 1: Change in IPSS score at 3 Months

This endpoint will be measured by the change of IPSS between the baseline and 3 months post-procedure. A therapeutic responder is defined as a subject who has an IPSS improvement of ≥ 40%.

The study is considered a success if at least 50% of the subjects are considered responders.

3.3.2 Primary Safety Endpoint 1: Major Device or Procedure Related Complications at 3 Months

A major device related complication is defined as any of the following device or procedural related serious adverse events at 3 months:

- Device or procedure related new onset severe urinary retention lasting > 14 consecutive days post-healing
- Device or procedure related unresolved new onset stress urinary incontinence by 90 days
- Device or procedure related bleeding requiring transfusion

3.3.1 Secondary Endpoint 1: Average Improvement of IPSS Compared to Baseline at each of the major follow up timepoints at or after 3 months

3.3.2 Secondary Endpoint 2: Change in Peak urinary flow rate (Qmax)

3.3.3 Secondary Endpoint 3: Proportion of subjects whose IPSS improvement is ≥ 30%, 40%, 50% and 75% post-treatment at each of the major follow up timepoints at or after 3 months

3.3.4 Exploratory Endpoints

- E1: Change in pain score
- E2: Change in IIEF (International Index of Erectile Function)
- E3: Change in EQ-5D quality of life
- E4: Subject satisfaction
- E5: Procedure parameters
- E6: Change in MSHQ-EjD

4 SUBJECT SELECTION

[redacted]

4.1 Inclusion Criteria

1. Male subject > 50 years of age who has moderate-to-severe LUTS (IPSS score of ≥ 13) and is a candidate for interventional therapy
2. LUTS felt to be secondary to an enlarged prostate (henceforth termed LUTS/BPH)

3. Peak urinary flow rate (Qmax) ≥ 5 mL/sec and ≤ 15 ml/sec with minimum voided volume of ≥ 125 ml
4. Post-void residual (PVR) ≤ 250 ml
5. Prostate volume 20 - 80 gm as determined by TRUS
6. Prostatic urethra length is 35 – 55 mm as determined by TRUS
7. Able to complete the study protocol in the opinion of the investigator

4.2 Exclusion Criteria

1. Interested in maintaining fertility and unwilling to use protected sex for the first 30 days post treatment
2. Unwilling to abstain or use protected sex for ninety (90) days post treatment if sexual partner is of child bearing potential
3. Presence of a penile implant or stent(s) in the urethra or prostate
4. Any prior minimally invasive intervention (e.g. TUNA, Balloon, Microwave, Rezūm, UroLift) or surgical intervention of the prostate
5. PSA > 10 ng/ml unless prostate cancer is ruled out by biopsy. If PSA is > 4 ng/ml and ≤ 10 ng/ml, prostate cancer must be ruled out to the satisfaction of the investigator via additional tests including digital rectal exam (DRE) and/or biopsy
6. Confirmed or suspected malignancy of prostate or bladder
7. Active or history of epididymitis within the past 3 months
8. Previous pelvic irradiation or radical pelvic surgery
9. Documented active urinary tract infection (UTI) by culture or bacterial prostatitis within last year documented by culture (UTI is defined as >100,000 colonies per ml urine from midstream clean catch or catheterization specimen)
10. Visible hematuria with subject urine sample without known contributing factor
11. Neurogenic bladder or sphincter abnormalities or neurological disorders that might affect bladder or sphincter function
12. Previous or current diagnosis of urethral strictures, bladder neck contracture or detrusor muscle spasms
13. Use of beta blockers, antihistamines, anticonvulsants, or antispasmodics within 1 week prior to treatment unless there is documented evidence of stable dosing for last 6 months (no dose changes)
14. Use of alpha blockers, antidepressants, anticholinergics, androgens, daily tadalafil or gonadotropin-releasing hormonal analogs (prescribed for BPH) within 3 weeks prior to treatment
15. Use of 5-alpha reductase inhibitor within 6 months prior to treatment
16. Incidence of spontaneous urinary retention within 6 months prior to baseline assessment
17. Post-void residual volume > 250 ml or catheter dependent bladder drainage
18. Overactive bladder (OAB) or urge incontinence
19. Known poor detrusor muscle function (e.g. Qmax < 5 ml/sec)
20. Current bladder stones or prostatic calculi
21. Biopsy of prostate within 30 days prior to procedure or planned within 30 days following the procedure

22. History of cancer in non-genitourinary system which is not considered cured (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered cured if there has been no evidence of cancer within five years
23. History of clinically significant comorbidities or presence of unstable conditions (e.g. cardiovascular, lung, renal [serum creatinine > 2.0 mg/dl], hepatic, bleeding disorders, or metabolic impairment) that may confound the results of the study or have a risk to subject per investigator's opinion
24. Any cognitive disorder that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affects the ability to complete the study quality of life questionnaires
25. Expected life expectancy < one year
26. Unable or unwilling to sign the Informed Consent Form (ICF) and/or comply with all the follow-up requirements
27. Currently enrolled in or plan to enroll in another investigational clinical trial for any disease except for observational only study
28. In the opinion of the investigator, it is not in the subject's best interest to participate in the study
29. Current treatment with anti-coagulants (e.g., warfarin or enoxaparin) or anti-platelet medications other than aspirin (e.g., clopidogrel)
30. Anatomy, e.g. presence of false passage or size of meatus, is not suitable for treatment in this study
31. Device that corresponds with the subject's prostate size per the IFU is not available
32. Intravesical prostatic protrusion (IPP) > 1 cm
33. Current uncontrolled diabetes (hemoglobin A1c > 7%)
34. Unable or unwilling to provide all the protocol-required semen samples
35. Sensitivity to paclitaxel, on medication that may have negative interaction with paclitaxel, or contraindicated for systemic paclitaxel

5 SITE SELECTION

Sites will be selected based on the availability of the subject pool to be included in the study and the sites' ability to perform the research with sufficient resources and in compliance with GCP guidelines.

In addition, the sites must be able to comply with any country-specific requirements as well as other requirements specified by their respective ethics committee (EC).

6 PHYSICIAN SELECTION

Physicians selected must have experience in performing cystoscopy and endoscopic treatment of BPH. Selected physicians will be trained in the use of Urotronic's pre-dilation balloon catheter and Optilume BPH Prostatic Drug Coated Balloon Dilation Catheter prior to enrolling subjects. The primary investigator at each site will ensure that only trained sub-investigators who satisfy the physician selection criteria can perform the study interventional procedure.

Healthcare professionals or site staff that assist or perform the follow-up evaluations do not need to be trained on the use of the device but must be delegated and trained to perform the follow-up visit procedures.

7 STUDY PROCEDURES

7.1 Pre-screening, Screening, and Baseline

The site may pre-screen potential subjects by reviewing medical records to identify potential study subjects. Once identified, these subjects are approached for the study and consented. The site may not initiate any study specific (non-standard of care) procedures without first obtaining informed consent.

All baseline testing and evaluations must be done as close to the time of scheduled treatment as possible and repeated if needed. Any required procedures performed before obtaining informed consent as part of the standard of care may be used in lieu of the study tests.

[redacted]

8. [redacted]

7.2 Subject Enrollment

Only subjects who meet the entrance criteria will be eligible to be enrolled and participate in the study.

Once it is determined that a subject meets the enrollment criteria (except for the use of the concomitant medication), the subject will be given an informed consent to read. If the subject is on BPH medication, they will then go through a washout period. Subjects who cannot tolerate a drug washout or are considered high risk from the drug washout should be excluded from the study. If the subject successfully goes through the washout period and still meets the entrance criteria, the

subject will be eligible to be enrolled. Screening information will be sent to the Study Principal Investigator (PI) for review and approval. After the subject provides informed consent, is approved by the Study PI, and is confirmed to meet all the entrance criteria, the subject will be considered enrolled and assigned a unique identification code (ID).

7.3 Concomitant Therapy

Therapy (medication and non-medication therapies) not restricted by protocol may be used during the study for the treatment or prevention of disease or to maintain good health. However, the subjects should not take concomitant medications that affect the urinary symptoms which might confound the study result, per physician's discretion.

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7.5 Scheduled Follow-up Evaluations

During the post-procedure period, investigators are encouraged to follow the current American Urological Association (AUA) guidelines in managing their subjects for the detection of prostate cancer in addition to the required evaluations in this protocol.

The following evaluations will be completed at each visit as indicated in Table 5. All subjects will be evaluated at baseline, immediately post-procedure, at Foley removal, 2 weeks, 30 days, 3 months, 6 months and 1 year post-procedure. [redacted]

Table 5: Scheduled Evaluations and Follow Up

Study Visit	Baseline	Intra-Op	24 hrs*	Foley Removal	4 Days*	2 Weeks	30 days	3 Months	6 Months	1 Year	Annual (Up to 5 years)	Unscheduled
Visit Windows	w/in 30 days†	Prior to discharge	±3 hrs	≥ 48 hrs	± 1 day	+3 days	±7 days	±14 days	±30 days	±30 days	±30 days	
Informed Consent	√											
Medical and genitourinary history	√											
Physical exam	√††					√	√	√	√	√	√	optional
Blood Analysis†††	√					√	√	√	√	√	√	optional
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]							
Prostate specific antigen (PSA)	√									√	√	
TRUS	√							√				
Cystoscopy	√	√						√				optional
Balloon Dilation		√										
Uroflow (Qmax + PVR)	√					√	√	√	√	√	√	optional
Urine Analysis	√			√		√	√	√	√	√	√	optional
Urine Culture	√			optional		optional	optional	optional	optional	optional	optional	optional

Study Visit	Baseline	Intra-Op	24 hrs*	Foley Removal	4 Days*	2 Weeks	30 days	3 Months	6 Months	1 Year	Annual (Up to 5 years)	Unscheduled
Visit Windows	w/in 30 days†	Prior to discharge	±3 hrs	≥ 48 hrs	± 1 day	+3 days	±7 days	±14 days	±30 days	±30 days	±30 days	
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[redacted]						[redacted]	[redacted]		[redacted]			
IPSS**	√					√***	√	√	√	√	√	optional
BPH Impact Index**	√					√	√	√	√	√	√	optional
EQ5D**	√					√	√	√	√	√	√	optional
MSHQ-EjD**	√						√	√	√	√	√	optional
Sexual function (IIEF)**	√						√	√	√	√	√	optional
Pain scale**	√	√****		√		√	√					
Subject Satisfaction Questionnaire								√				
Adverse event(s)		√	√	√	√	√	√	√	√	√	√	√

Study Visit	Baseline	Intra-Op	24 hrs*	Foley Removal	4 Days*	2 Weeks	30 days	3 Months	6 Months	1 Year	Annual (Up to 5 years)	Unscheduled
Visit Windows	w/in 30 days†	Prior to discharge	±3 hrs	≥ 48 hrs	± 1 day	+3 days	±7 days	±14 days	±30 days	±30 days	±30 days	
All Medication(s) used	√ (prior BPH medications and all current)	√ (since the previous visit)	√ (since the previous visit)			√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)

* Only for subjects participating in the PK cohort

** If multiple responses to the same questionnaires are available for each visit window, the last questionnaire will be used to qualify for the study

*** IPSS (acute) questionnaire should be used at the two week follow-up visit

**** Intra-operative pain scale must be done post-procedure while the subject is in recovery

† Cystoscopy and TRUS that were done within 60 days prior to the procedure may be used for the study baseline. Urine analysis and urine culture must be conducted within 14 days prior to the procedure

†† Baseline physical exam also includes demographics, height, weight and vital signs

††† Blood analysis includes complete blood count (hemoglobin, hematocrit, platelets, red blood cell count and white blood cell count) with differential (absolute neutrophils, lymphocytes, monocytes, eosinophils and basophils) and blood chemistry [glucose, calcium, protein (albumin, total protein), Electrolytes (bicarbonate, chloride, sodium, potassium), Kidney (blood urea nitrogen, creatinine), Liver (alkaline phosphatase, alanine amino transferase, aspartate amino transferase, bilirubin)]

7.6 Unscheduled Follow-up Visits

If subjects are seen for unscheduled/interim visits because of an AE, appropriate Case Report Form(s) (CRF), including the AE CRF, will be completed. At the investigator's discretion, some of the evaluations and tests may be repeated if indicated. The Sponsor requests that if any additional tests or procedures listed within this protocol are performed during an unscheduled visit, the investigator should provide the results on the Unscheduled Visit CRF(s).

7.7 Lost to Follow-up

If a subject fails to comply with follow-up visits, the investigational site must make at least three repeated attempts to contact the subject. Each attempt to contact the subject and the method used (e.g., telephone contact, registered letter) must be documented in the subject's records.

If a subject misses one of the follow-up visits, but is present at the subsequent follow-up, the subject should be queried retrospectively for basic information (e.g., AEs); however, the IPSS and other questionnaires will be collected prospectively only. The missed visit must be documented on a Protocol Deviation CRF.

7.8 Subject Withdrawal from Study

7.8.1 Voluntary Withdrawal

A subject may voluntarily withdraw from the study at any time. If a subject officially withdraws from the study, the investigator must ensure that the reason for the withdrawal is documented. If the subject had an AE, the subject should be followed until the resolution of the AE, if possible. Data from these subjects will be included in the analysis up to the point of each subject's withdrawal.

7.8.2 Data Withdrawal Due to Exclusion Criteria

A subject's data may be excluded from the analysis if the subject is later found not to meet one or more major entrance criteria. However, these subjects will continue to be followed unless instructed otherwise by the EC. The major entrance criteria that would cause the withdrawal of the subjects' data are:

- Failure to obtain an informed consent prior to treatment;
- Subject had bladder or sphincter dysfunctions or anything else that would confound the results;
- Subject had a psychiatric or cognitive disorder that prevents him from adequately answering the study questionnaires.

The decision to exclude the subject's data from analysis will be documented on the End of Study CRF.

7.8.3 Involuntary Withdrawal

A subject also may be withdrawn by the investigator if the subject's participation in the study will have a negative effect on the safety of the subject. Data obtained up to the date of the subject's withdrawal will be included in the study, if applicable.

7.9 End of Study

Subjects receiving the Urotronic DCB procedure may exit the study at the end of the study, either when the subject has completed the 1-year or 5-year follow-up visit or the study is discontinued by the Sponsor, whichever comes first, unless the subject opted to find an alternative treatment.

If a subject receives additional BPH therapy, ongoing follow-up will be limited to general health information at the planned follow-up visits after receiving this therapy. General health information may include vital status, adverse events that have occurred, or additional BPH therapies that have been received since the last subject contact. General health follow-up information may be collected remotely.

An End of Study CRF will be completed at the time the study is completed, discontinued, or lost to follow-up for each subject.

8 SUBJECT EVALUATION DESCRIPTION

Follow-up evaluations are expected to be conducted via an in-office visit to allow for collection of all the required follow-up assessments. Remote follow-up visits may be conducted in the event an in-person visit is not feasible (e.g., due to COVID-19), but the inability to conduct assessments as described in Table 5 that require an in-office visit must still be reported as a protocol deviation as described in Section 13.8.3. Urinalysis, urine culture and uroflow measurements collected at non-study sites as standard of care may be utilized if the subject is unable to visit the study site without the need to document a protocol deviation unless the testing does not meet the requirements of the protocol (e.g., voided volume < 125 ml).

If a visit is unable to be performed in-person due to COVID-19 restrictions, it is encouraged that sites complete a remote visit within the visit-window to assess subject safety and administer questionnaires at a minimum. The subject should be brought in for an Unscheduled visit as soon as individual and public health concerns allow. Questionnaires should be re-administered at this Unscheduled visit.

8.1 Subject Questionnaires

All questionnaires are preferably self-administered and will be completed at baseline (with the exception of the Subject Satisfaction Questionnaire) and at required follow-up visits. If the assessment is required to be conducted remotely (e.g., due to COVID-19 limitations), the questionnaires may be mailed to the subject for completion prior to phone/telemedicine follow up, and the subject may be queried for understanding of the questions during the visit. If subject

compliance is uncertain, the IPSS, VAS, and Subject Satisfaction questionnaires may be interview administered at the time of the phone follow up. If a questionnaire is interview administered, this should be recorded in the source documentation. Evidence exists that interview administration produces equivalent results for these questionnaires.[1,2]

Questionnaires completed at baseline will be compared to those completed at follow-ups to assess the effect of treatment. The major instruments and assessments administered are described in this section.

8.1.1 IPSS (Standard)

The International Prostate Symptom Score (IPSS) contains the well-validated, highly reliable and responsive American Urological Association symptom score (AUASS) assessment to identify the severity of BPH symptoms.

The first seven questions in the IPSS address frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency, and scored on a 6-point scale (0 to 5). The IPSS can be interpreted as follows: 0-7 mildly symptomatic, 8-19 moderately symptomatic, and 20-35 severely symptomatic.

The IPSS also includes the following eighth question that is designed to assess the degree of "bother" associated with the subject's urinary symptoms: "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?" Answers range from "delighted" to "terrible" (0-6). This question correlates well with the overall BPH symptom score and summarizes the impact of urologic symptoms on quality of life.

The standard IPSS will be administered at baseline and at each follow-up visit beginning with the 30 Days Visit.

8.1.2 IPSS (Acute)

The acute IPSS is the same as the standard IPSS except that the questions refer to the subject's condition in the past week instead of the past month. This IPSS will be administered at the Two Week follow-up visit and if indicated, at unscheduled visits.

8.1.3 BPH Impact Index

The BPH Impact Index is a self-administered questionnaire that measures the impact of BPH symptoms on the subjects' quality of life. The questionnaire assesses physical discomfort, anxiety/worry, bothersome, and effect on activities of daily living.

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[1] Plante M, Corcos J, Gregoire M, et al. The International Prostate Symptom Score: Physician vs Self-Administration in the Quantification of Symptomology. *Urology*. 1996;47:326-8.

[2] Von Korff M, Jensen MP, Karoly P. Assessing Global Pain Severity by Self-Report in Clinical and Health Services Research. *Spine*. 200;25(24):3140-51.

The BPH Impact Index will be administered at baseline and at each follow-up visit beginning with the Two Week Visit.

8.1.4 International Index of Erectile Function

The International Index of Erectile Function (IIEF) is a standardized, validated, self-administrated questionnaire that is used to assess the subject's erectile function. The Sexual Health Inventory for Men (SHIM) is part of the IIEF and consist of 5 questions. This is sometimes called IIEF-5 and is used as a diagnostic test for erectile dysfunction and impotence.

The standard IIEF will be administered at baseline and at each follow-up visit beginning with the 30 Days Visit.

8.1.5 EQ-5D

EQ-5D™ is a standardized instrument for use as a measure of health outcome. EQ-5D-5L is a self-reported generic preference-based measure of health, developed by the EuroQol Group. The instrument can be applied to, and has been shown to be valid for, a wide range of health conditions. The EQ-5D has been used in many studies as a way of capturing the health-related quality of life of patients, trial participants and the general public.

The EQ-5D will be administered at baseline and at each follow-up visit beginning with the Two Week Visit.

8.1.6 MSHQ-EjD

MSHQ-EjD is the four-item version of Male Sexual Health Questionnaire (MSHQ) to assess ejaculatory dysfunction (EjD). It is a self-reported questionnaire that contains three ejaculatory function items and one ejaculation bother item.

The MSHQ-EjD will be administered at baseline and at each follow-up visit beginning with the 30 Days Visit.

8.1.7 Subject Pain Questionnaire

The Visual Analog Scale (VAS) pain score (1 to 10 scale) will be used to access the subject’s pain.

The pain scale will be administered at baseline, post-procedure while the subject is in recovery, following Foley removal and at the 2 Weeks and 30 Days Visits.

8.1.8 Subject Satisfaction Questionnaire

This questionnaire is specific to the Urotronic DCB procedure on the treatment of moderate-to-severe LUTS/BPH and will measure overall satisfaction with the procedure, recommendation of treatment to friends/family and if the subject would undergo the treatment again if symptoms were to recur within 1 year.

The Subject Satisfaction Questionnaire will be administered at the 3 Months Visit.

8.2 Uroflowmetry

Subjects will be asked to hydrate and refrain from voiding for two hours prior to each uroflowmetry. Hydration may be achieved by asking the subject to drink 2 or more cups of non-caffeinated fluids.

A bladder scan is recommended to be performed prior to voiding to ensure the subject has a bladder volume of at least 250 ml.

Outcomes will be recorded for each qualified void on the CRFs and the strip recordings collected. Voiding data will be obtained with the subjects in the standing or sitting position, voiding into the uroflow instrumentation. The uroflow meter will provide the following information:

- Voided volume (≥125 ml required for a valid test)
- Peak flow rate (Qmax), averaged over a 2-second interval
- Average flow rate
- Voiding time

8.2.1 Peak Flow Rate (Qmax) Measurement

The recommendation for determining the Qmax reading is to apply the 2-second rule to improve consistency. This would avoid artifacts in the reading.

8.2.2 Post Void Residual Urine Volume

Following uroflowmetry, residual urine volume in the bladder shall be assessed by either bladder scanner ultrasound or catheterization. The same method must be used pre- and post-treatment.

8.3 Cystoscopy

A screening cystoscopy with video will be performed to confirm the presence of obstructive BPH and to estimate the BPH severity.

Flexible or rigid cystoscope will be used to facilitate the DCB procedure.

A cystoscopy with video will also be performed at the 3-month follow-up visit concentrating on the prostatic urethra.

8.4 TRUS

Transrectal Ultrasonography (TRUS) at baseline is required to determine the prostate size and to measure any intravesical prostatic protrusion (IPP).

A TRUS will also be performed at the 3-month follow-up visit.

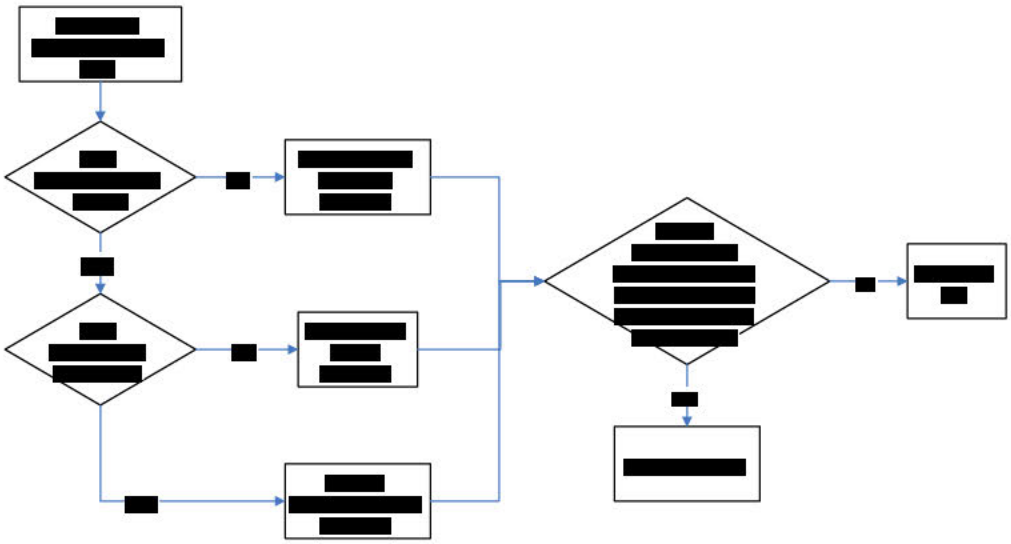
9 STATISTICAL CONSIDERATIONS

The details of the analysis is provided in the statistical analysis plan. The treatment will be considered a success if the primary efficacy endpoint is met and there are no safety concerns.

[redacted]

[redacted]

[redacted]



[redacted]

- [redacted]

[redacted]

[redacted]

11 TRAINING

The Sponsor will be responsible for training of appropriate clinical site study personnel. To ensure proper procedural technique, uniform data collection and protocol compliance, the Sponsor will present a formal training session to personnel at each study site. At this training session, the study protocol, techniques for the identification of eligible subjects, instructions on data collection, schedules for follow-up, and regulatory requirements will be reviewed.

12 DATA MANAGEMENT

[redacted]

12.2 Central Database

All study documentation will be collected and compiled in a central database. Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the central database.

13 STUDY RESPONSIBILITIES AND MANAGEMENT

13.1 Investigator Responsibilities

Each investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, EC requirements, and applicable laws and regulations. Also, Investigators may not begin enrollment until Sponsor or its designee receives and approves (when necessary) the following documents:

- Signed Investigator Agreement
- Financial disclosure forms for all participating investigators
- EC roster
- EC protocol and ICF approvals
- Investigators' current curricula vitae (CV)
- Signed Site Delegation Log

It is acceptable for Investigators to delegate one or more of the study functions to an associate or Co- or Sub-Investigator, or a trained Study Coordinator; however, the Principal Investigator remains responsible for the proper conduct of the clinical investigation, including obtaining and documenting proper study informed consent, collecting all required data, submitting accurate and complete CRFs, etc.

At each study site, appropriate procedures must be followed to maintain subject confidentiality according to appropriate local regulations. Each site may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each Investigator is responsible for obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant subject privacy laws.

The study is not transferable to other sites attended by the Investigator unless prior approval is obtained from the appropriate EC and the Sponsor.

[redacted]

13.3 Ethics Committee (EC)

Investigators must submit the study protocol to their respective Ethics Committee (EC) and obtain the EC's written approval before being allowed to conduct and participate in the study. Each Investigator is responsible for fulfilling any conditions of approval imposed by their respective EC, such as regular reporting, study timing, etc. Investigators will provide the Sponsor or its designee with copies of such approvals and reports.

13.4 Informed Consent Form (ICF)

The Sponsor will provide a template informed consent form (ICF) to each study site for EC submission. The template may be modified to suit the requirements of the individual study site but the Sponsor must pre-approve all changes to the ICF prior to initial submission to the EC.

Each Investigator or assigned designee must administer this approved ICF to each prospective study subject, and obtain the subject's signature or a legally-approved designee's signature along with the

date of consent prior to enrollment in the study. The ICF must be obtained in accordance with the applicable guidelines of the Declaration of Helsinki, or local regulations and laws, whichever represents the greater protection of the individual. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and also be informed that withdrawal from the study will not jeopardize their future medical care. A copy of their signed ICF must be given to each subject enrolled in the study. The institutional standard subject consent form does not replace the study ICF.

13.5 Case Report Forms (CRFs)

The Sponsor will provide standardized case report forms (CRFs) for each individual subject. The CRFs will be electronic (EDC, 21 CRF Part 11 compliant), will be used to record study data, and are an integral part of the study and subsequent reports.

The electronic CRFs for individual subjects will be provided by the Sponsor via a web portal. After the data have been monitored and submitted, corrections will be initiated via a data query or Data Clarification Form (DCF) to be completed by study site personnel. This DCF also will be done electronically via the web portal. Electronic CRFs must be approved and signed by the Investigator using his/her electronic signature.

13.6 Records

Each Investigator must maintain the following accurate, complete, and current records relating to the conduct of the study investigation. The final responsibility for maintaining such records remains with the Investigator. These records include, but not limited to:

- All signed agreements;
- EC approval letter(s);
- Signed ICFs;
- Records of AEs, including supporting documents;
- Records of protocol deviations, including supporting documents;
- Records showing receipt, use and disposition of all investigational devices, including:
    - Date, quantity, model, lot and serial numbers (if applicable) of devices received,
    - Name of person(s) who received, used or disposed of each device,
    - The number of devices returned to the Sponsor and the reason(s) for return;
- All correspondence related to the study;
- Records of each subject's case history, including study-required CRFs, signed ICF, all relevant observations of AEs, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, etc.;
- Study personnel visit log;

- Signature authorization and delegation log; and,
- Any other records that applicable regulation requires to be maintained.

13.7 Reports

Table 6 lists those reports that are the investigator's responsibility to deliver to the Sponsor. Each study investigator must follow the EC reporting requirements for their respective site. If applicable regulations or EC requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 6: Reports Required from Investigators to Sponsor

Type of Report	Prepared by PI for	Notification Time Frame
UADE	Sponsor, EC	Within 24 hours of knowledge
Death	Sponsor, EC	Written reports (e.g., via e-mail) within 24 hours of knowledge
SAE	Sponsor EC, if required	Within 24 hours of knowledge Per EC requirement
Device malfunction with clinical sequelae	Sponsor EC, if required	Within 48 hours via written communication. Return the device to Sponsor within 48 hours or as requested.
Serious protocol deviations (e.g., ICF not obtained, to protect the life or physical well-being of a subject in an emergency)	Sponsor EC, if required	Within 5 working days of knowledge Per EC requirement
Withdrawal of EC approval	Sponsor	Within 5 working days of knowledge
Progress report	Sponsor, EC	As required by EC
Final report	Sponsor, EC	Within 3 months of study completion or termination
Note: Each EC may require more stringent reporting requirements that those listed in this table.		

13.8 Sponsor Responsibilities

Urotronic, Inc. is the Sponsor of this study. The Sponsor's responsibilities in the study include:

- Selecting the Principal Investigator(s), all clinical investigators and study sites, and other consultants (e.g., monitors) who participate in the study.
- Provide study protocol, device, and GCP training to participating study sites, in quantities sufficient to support study activities, per agreements executed with the study sites.
- Select all qualified clinical Investigators and study sites and other consultants (e.g., the study monitors) who participate in the study.
- Provide financial support to each study site.
- Follow/promote all regulatory standards per appropriate regulations for study sites, core laboratories, and other participants, and ensure compliance by periodically monitoring sites.
- Ensure completion of site monitoring of clinical data at each clinical study site.
- Retain ownership of all clinical data generated in this study, and control the use of the data for appropriate purposes only.
- Review and approve publication of study results in the literature.

13.8.1 Confidentiality

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential according to the country's patient confidentiality regulations. Data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. Investigators will consent to visits by Sponsor's staff and its authorized representatives, as well as by the FDA or local governmental body, to review the study subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., cystograms).

13.8.2 Amending the Investigational Study Protocol

Neither any Investigator nor the Sponsor will modify the Investigational Protocol without first obtaining concurrence of the other in writing. All changes to the Investigational Protocol must be submitted to the EC for review and approval unless the changes do not affect the subject's safety or the integrity of the data (e.g. administrative changes). Any change that would require alteration to the ICF must receive approval from the applicable EC prior to implementation. Following approval, any Investigational Protocol amendment must be distributed to all protocol recipients at the site.

13.8.3 Protocol Deviations

A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. An investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete

scheduled visits as required by the protocol, would be considered protocol deviations. These type of deviations are reported to the Sponsor and in accordance with the EC policy.

A Protocol Deviation CRF must be completed by the site for each study protocol deviation (e.g., failure to obtain informed consent, enrolling a subject who does not meet inclusion / exclusion criteria, not performing required testing, missed follow-up window, etc.). Those deviations from the protocol that occur due to limitations related to the COVID-19 pandemic should be reported in the study database for each applicable visit (i.e., not in bulk), with the type of deviation describing how the specific activity failed to follow protocol-specified requirements and the reason for deviation describing how COVID-19 impacted the ability to perform the specific activity.

An Investigator must notify the Sponsor and the reviewing EC of any deviation from the Study Protocol that was done to protect the life or physical well-being of a subject. Such notice should be given as soon as possible, but no later than five (5) working days after the emergency occurred.

13.8.4 Protocol Deviation Notification/Approval to EC/Sponsor before Implementation

A protocol deviation may be a limited prospective exception to the protocol (e.g. agreement between Sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria due to out of window historical data). This type of deviation initiated by the clinical investigator must be reviewed and approved by the EC and the Sponsor prior to implementation. This type of deviation can be used for historical data that is out of window (i.e., due to date of screening visit). The objective is to prevent subjects from being subject to repeat and possible invasive testing. These type of deviations are only approved if they do not impact data integrity or put subjects at unreasonable risk.

13.8.5 Site Noncompliance and Nonperformance

Repeat serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations are noted, the Sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place at the site to reduce further deviations.

After a site completes all required approvals and training, a site initiation visit will be conducted as a final check of the site readiness. If a site is not able to enroll its first subject 3 months after "Ready to Enroll" status, the Sponsor may elect to terminate the investigational site and allocate the slot to another candidate site.

14 STUDY ADMINISTRATION

14.1 Monitoring Procedures

It is the responsibility of the study Sponsor to ensure that proper monitoring of this investigation is conducted. Appropriately trained personnel, appointed by the study Sponsor, will complete any monitoring that is done. The monitoring will be the responsibility of Sponsor study personnel with an address as listed in the title page of this document. Monitors will ensure that the investigation is conducted in accordance with:

- The signed Investigator's Agreement
- The Investigational Plan
- Appropriate laws and regulations
- Any conditions of approval imposed by the reviewing EC and/or other regulatory agencies

The clinical study will be monitored according to the guidelines summarized below. The Sponsor may choose to perform random inspections throughout the study as an element of quality assurance. Investigators shall allow auditing of their clinical investigation procedures.

A study specific Monitoring Plan is created and implemented to standardize monitoring activities across centers and ensure human subject protection and verify data integrity. The monitors shall receive study specific and SOP training prior to conducting any monitoring visits. Study monitors are selected based on their training, qualifications and experience to monitor the progress of an investigation. Study monitors may be Sponsor's employees or representatives. This study monitoring will include a site qualification, study initiation, interim, and close out visits. Not all sites will require a qualification visit. The reason for waiving the visit (e.g. participation in a previous Urotronic clinical study) will be documented in a Note to File. All study monitors will be required to follow the monitoring plan and monitoring standard operating procedures (SOPs).

[redacted]

14.1.1 Monitoring Visit

The following factors will be taken into account when determining the frequency of the monitoring visits: subject accrual rate at each center, total number of subjects enrolled at each center, and Clinical Investigation Plan compliance at each center. [redacted]

[redacted]

Monitors may ensure the clinical investigators have and continue to have staff and facilities to conduct the clinical investigation safely and effectively. Monitors may conduct the following monitoring activities throughout the study:

- Verification that the current EC-approved informed consent was signed and dated by each subject prior to participating in the study required procedures.
- Verification of documentation in the subject's record that informed consent was signed prior to initiation of the study procedures and that a copy of the signed and dated consent was provided to the subject.
- Source documentation verification by reviewing the CRFs against source documentation for accuracy and completeness of information.
- Verification that the device is being used according to the Clinical Investigation Plan, Instructions for Use and, all malfunctions/ IFU deficiencies are reported. as required.
- Verification that subjects met study enrollment criteria.
- Confirmation that the study is being conducted according to the Clinical Investigation Plan and applicable regulations.
- Verification that study deviations are documented and reported.
- Verification that the procedures for recording and reporting adverse events to the Sponsor are followed.
- Ensuring proper error correction.
- Verification of training documentation of all study personnel participating in study related activities.
- Reviewing all correspondence and regulatory documents, including confirmation of EC-approved Clinical Investigation Plan or amendments.
- Resolution of outstanding issues and completion of assigned tasks will be documented by the monitors.

Each monitoring visit will be documented via a monitoring report and follow-up letter. The follow up visit letter shall be sent to the Investigator to document issues identified, corrective actions and if applicable preventative actions. At subsequent visits the issues resolved shall be documented in this letter to demonstrate resolution.

14.1.2 Study Closure

Study closure is defined as a specific date that is determined by study completion and/or regulatory requirements have been satisfied per the Clinical Investigation Plan (CIP) and/or by decision of the Sponsor or EC. Study closure visits will be conducted at all enrolling clinical sites in order to review record retention requirements with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g., low subject enrollment, recent monitoring visit, etc.)

[redacted]

[redacted]

17 POTENTIAL DEVICE CHANGE

Future product line extensions (e.g. larger diameter or longer length balloon) or design changes may be introduced into the study based on feedback from investigators. In addition, manufacturing changes may be introduced. All design and manufacturing process changes will be performed under the Sponsor's design control process and fully tested to ensure that it meets specifications. Significant changes that may affect the device safety or performance will be provided to the EC as a supplemental application.

The device design or process changes will be evaluated to ensure that they continue to meet the product specifications.

18 PUBLICATION POLICY

The data and results from the trial are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical trial. The Investigators will not use the clinical trial/investigation-related data without the written consent of the Sponsor for any other purpose than for clinical trial/investigation completion or for generation of publication material, as referenced in the Clinical Trial Agreement/Investigator Agreement.

The Sponsor acknowledges that the trial's Principal Investigators intend to publish a multi-center publication regarding the clinical trial/investigation results, and numerous secondary publications. The Sponsor must receive any proposed publication and/or presentation materials at least 30 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the Sponsor in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement/Investigator Agreement.

The Sponsor is responsible for determining whether to register the Clinical Investigation on www.clinicaltrials.gov. Institution(s) and/or Principal Investigator(s) shall not take any action to register the trial.

19 REFERENCES

[1] Hansen B, Flyger H, Brasso K, et al. Validation of the self-administered Danish prostatic symptom score (DAN-PSS-1) system for use in benign prostatic hyperplasia. Br J Urol. 1995;76:451-458.

[2] Barry MJ, Fowler FJ Jr, O'Leary MP, et al. Measurement committee of the American Urology Association. Med Care. 1995;22:AS145

[3] Vuichoud C and Loughlin KR. Benign prostatic hyperplasia: epidemiology, economics and evaluation. Can J Urol. 2015 (Internal Suppl):1-6

[4] Barry MJ, Fowler FJ Jr, O'Leary MP, et al. Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. Med Care. 1995 Apr;33(4 Suppl):AS145-55.

[5] McVary KT, Roehrborn CG, Avins AL, et al. Management of benign prostatic hyperplasia (BPH) http://www.auanet.org/guidelines/benign-prostatic-hyperplasia-(2010-reviewed-and-validity-confirmed-2014)