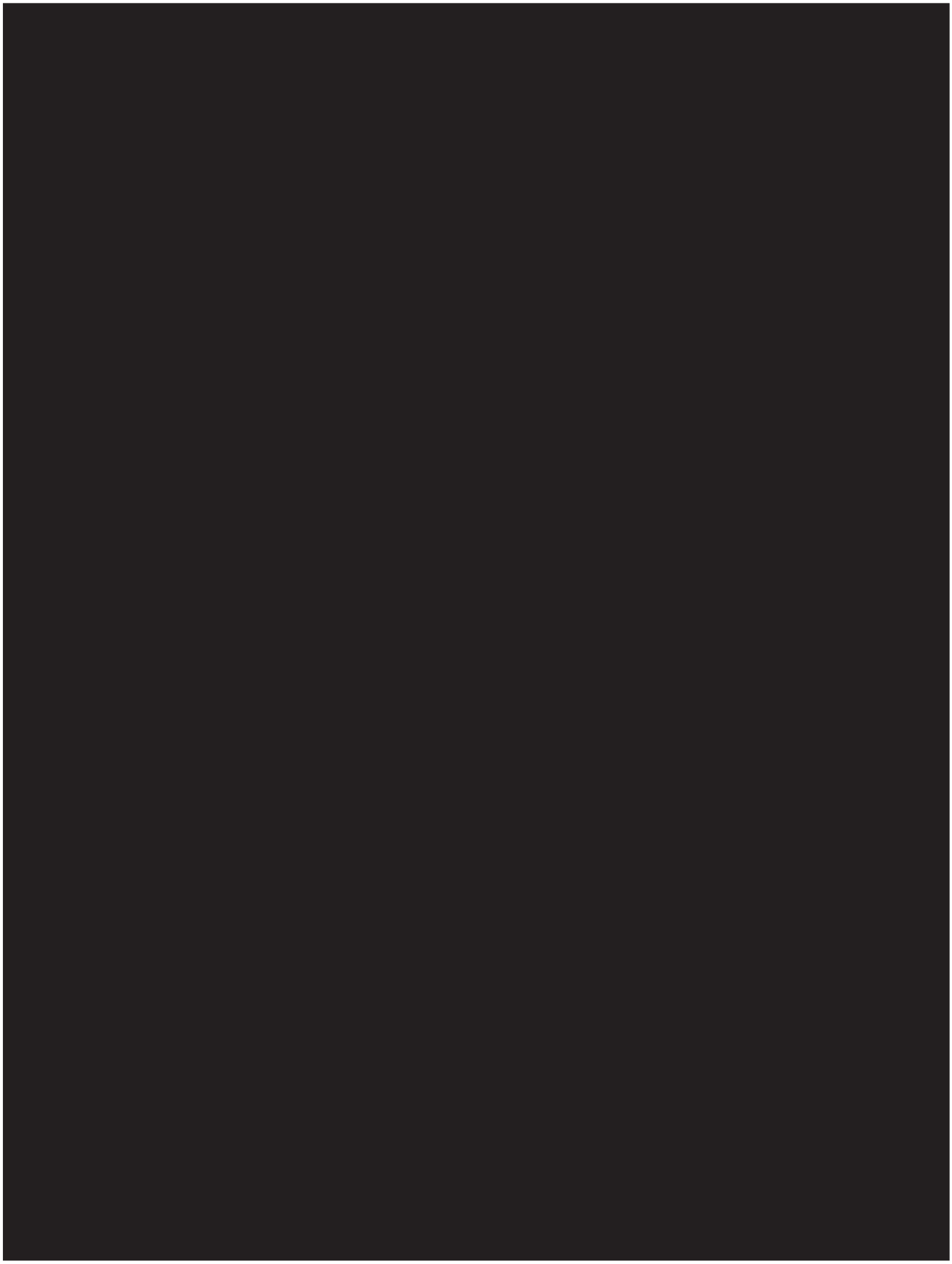


DSC016 Rev F

ROBUST I Pilot Study

Re-Establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease

August 11, 2017

DSC016 Rev F

NCT03014726

ROBUST I Pilot Study

Re-Establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease

PROTOCOL No. DSC016 Rev F

August 11, 2017

SPONSOR

Urotronic Inc

[redacted]

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

ROBUST I Pilot Study

Re-Establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease

PROTOCOL No. DSC016

Revision F

August 11, 2017

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 Principal Investigator Signature Date

_____

Site Principal Investigator

Printed Name

Protocol Summary

Title:	ROBUST 1 Re-Establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease
Objective:	The study described below is designed to determine the safety and effectiveness for drug-coated balloon (DCB).
Study Design:	Single arm, multicenter study
Enrollment:	Up to 50 Subjects
Target Subject Population:	1. Male subjects ≥ 18 years' old 2. Visual confirmation of stricture via cystoscopy or urethrogram 3. Single lesion anterior urethral stricture or bladder neck contracture less than or equal to 2 cm 4. One to three (1-3) prior diagnosis and treatment of stricture treatments (including self-catheterization) including DVIU, but no prior urethroplasty 5. Significant symptoms of stricture such as frequency of urination, dysuria, urgency, hematuria, slow flow, feeling of incomplete emptying, recurrent UTI's. 6. IPSS score of 13 or higher 7. Lumen diameter <12F by urethrogram 8. Able to complete validated questionnaire independently 9. Qmax <10 ml/sec
Follow-up:	5 days, 14 days, 30 days, 3 months, 6 months, 12 months, Annually up to 5 years
Endpoint 1	Rate of Treatment Related Serious Complication
Endpoint 2	Improvement in IPSS
Endpoint 3	Improvement LUTS Voiding Construct (Mundy PROM) Score
Endpoint 4	Stricture Recurrence Rate
Endpoint 5	Change in IIEF
Endpoint 6	Repeat Treatment Rate
Endpoint 7	Change in Qmax at 3 and 6 months

Endpoint 8	Paclitaxel content in blood, urine and semen
Endpoint 9	Stress Urinary Incontinence at <90 days and >90 days
Study and Data Management:	[redacted]
Study Monitors:	
Sponsor:	**Urotronic Inc** [redacted]

Table of Content

1 INTRODUCTION

1.1 Disease State Overview and Epidemiology

A urethral stricture is scarring in the urethra or surrounding tissue that narrows or blocks the passageway through which urine flows from the bladder. The stricture can result from inflammation, infection or injury, and is much more common in men than in women. The scarring can occur anywhere between the bladder and the tip or opening of the urethra. In addition to uncomfortable urinary symptoms such as reduced flow rate and frequent urination, a urethral stricture can lead to complications that include urinary tract infections, prostatitis, urinary retention and kidney damage. There were 1.5 million office visits from 1992 to 2000 in US for the treatment of urethral strictures, and resulted in $191 million in health care expenditures[11].

Initial therapy for strictures is frequently dilation, which involves either balloon or rigid dilation to open the urethral stricture and allow normal voiding to occur. The most common complication subsequently to dilation is stricture recurrence, possible with increased length, due to adjacent tissue damage[2]. Potential advantages of balloon dilation vs. sequential rigid dilation has been described[1,2]. Balloon dilation allows less discomfort and reduced risks because of less shearing force and reduced trauma, compared to the traditional rigid dilators[2]. More severe strictures can require surgical intervention for recurrent or long complicated lesions.

1.2 Stricture Diagnosis

Patients with lower urinary tract symptoms will have their urinary flow rate measured as part of the initial investigation of lower urinary tract symptom. In those who have a urethral stricture, the peak flow rate is typically low but with a flat flow pattern as shown in Figure 1-1.

This flow pattern is pathognomomic of a urethral stricture. The presence of the stricture must be diagnosed by urethrogram to determine the exact site and length of the stricture and its potential complications. Ultrasound may show a thickening of the bladder wall associated with longstanding outflow obstruction, and a presence of residual urine.

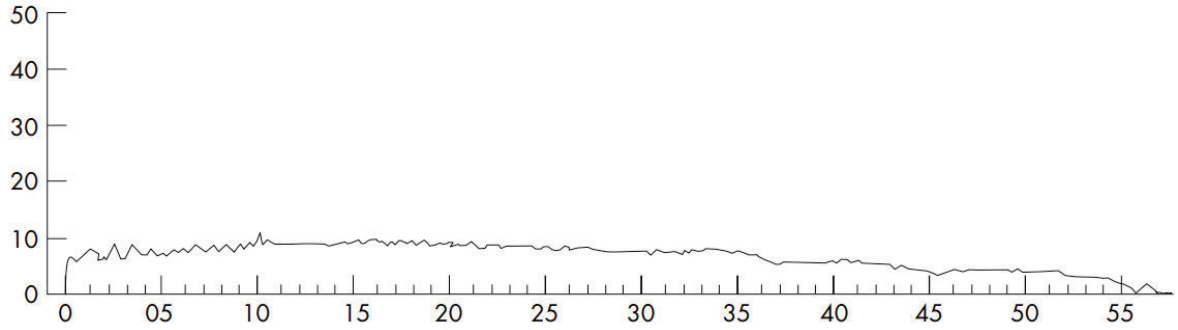


Figure 1-1: Characteristic Pattern for Urine Flow in the Presence of Stricture

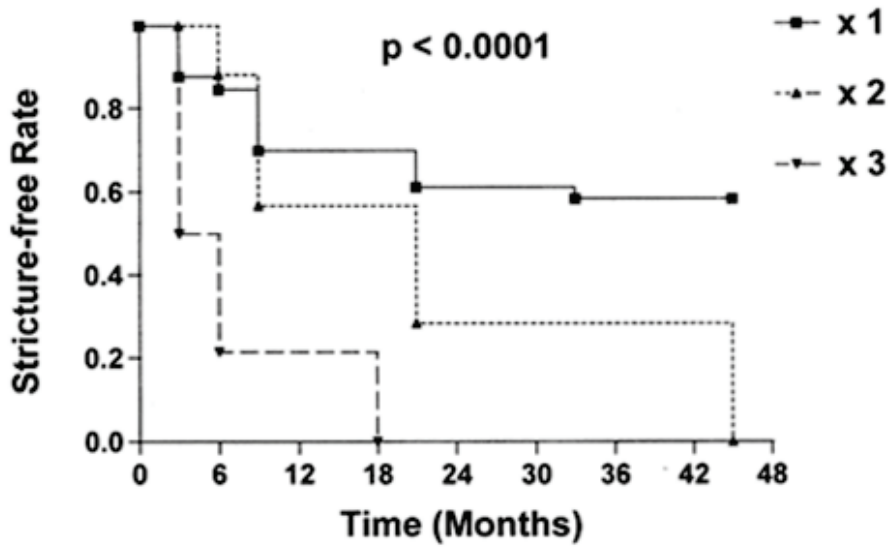
1.3 Current Standard of Care

Urethral strictures are still a common and challenging problem in urology. Although open urethroplasty remains the gold standard of care, it requires good expertise and is invasive.[11] The simplest form of treatment is urethral dilation using a balloon, or rigid dilators. The normal urethral caliber is 24-26F at the external urinary meatus, a little wider in the penile urethra, and about 36F at the bulbar urethra.[13]

The principle of urethral dilation is to stretch the urethral stricture up or to disrupt it to restore the urethral caliber to normal or thereabout. Urethrotomy and dilation are equally effective with expected cure rate of about 50% for short bulbar urethral strictures when first used. The success rate of repeated procedure is lower[13].

When strictures recur, they usually do so within weeks or months and almost always within two years. The expected recurrence rate reported are schematically summarized in Figure 1-2.

The following graph demonstrates the likelihood of success from a urethral dilation.



from The Journal of Urology: Volume 160(2) August 1998 pp 356-358

Figure 1-2: Stricture Recurrence Rate

The average time to recurrence for previously treated stricture is 3 months. Hazard function analysis showed that the risk of stricture recurrence was greatest at 6 months, whereas the risk of failure after 12 months was slight[11].

1.4 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 1-1. The improvement in restenosis rates led Urotronic to design a similar system to treat urinary strictures.

Table 1-1: 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
Urotronic DCB	TBD

1.5 Rationale for Study

Balloon dilation is the least invasive treatment for strictures. However, because of the nature of strictures, recurrence of the stricture (50% - 75%) following balloon dilation is common[2]. When stricture recurs after balloon dilation, treatment often progresses to more invasive treatments: internal urethrotomy is a slightly more invasive approach that involves an endoscopic incision of the stricture, but is not more effective than dilation[8,9,10]; urethroplasty is an open surgery for stricture disease that is more effective but far more invasive than dilation or internal urethrotomy. Urethroplasty is performed by a minority (~2%) of urologists and the vast majority of subjects are managed by less invasive therapies. Any improvement in technique or means of changing the natural history and progression of the disease would make a significant clinical contribution. The study described below is designed to determine the safety and effectiveness of the drug coated balloon (DCB).

2 DEVICE DESCRIPTION

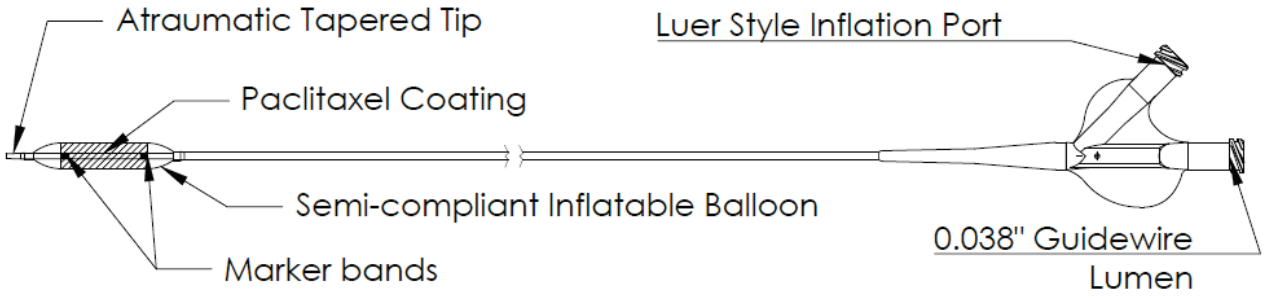


Figure 2-1: Urotronic 0.038" Paclitaxel-Coated Balloon Catheter

The Urotronic Drug Coated Balloon (DCB) is a 0.038" guidewire compatible over-the-wire catheter with a tapered atraumatic tip. The distal end of the catheter has a semi-compliant inflatable balloon coated with a proprietary coating containing the drug paclitaxel and carriers that facilitates the drug's transfer to the urethral wall upon inflation.

Paclitaxel is an anti-inflammatory and anti-proliferative drug commonly used to prevent arterial restenosis. The drug coating covers only the balloon body. Initially, the device will be available in one size only 24Fr diameter. Urotronic believes this size will be sufficient to treat the majority of the stricture. However, during the study, other sizes may be introduced if the need arises.

The device has two radiopaque marker bands that indicate the drug coated working length of the balloon under fluoroscopy. The device is provided sterile, and is intended for single use only.

3 STUDY OBJECTIVES AND DESIGN

3.1 Objective

The study described below is designed to determine the safety and effectiveness for drug coated balloon (DCB).

3.2 Study Design

This is a prospective, non-randomized, open label, multi-center pilot study. Up to 50 subjects will be enrolled and treated with the device at up to 5 clinical sites. Due to the significantly higher prevalence of strictures in men vs. women and the etiology of those strictures being different, the study will focus on male subjects with single anterior urethral stricture. Subjects will be followed up post-treatment at 5 days, 14 days, 30 days, 90 days, 180 days and 365 days, and then annually for up to 5 years. The annual follow up after the first year is optional. The diagnostic and treatment algorithm for the trial is shown in Figure 3-1.

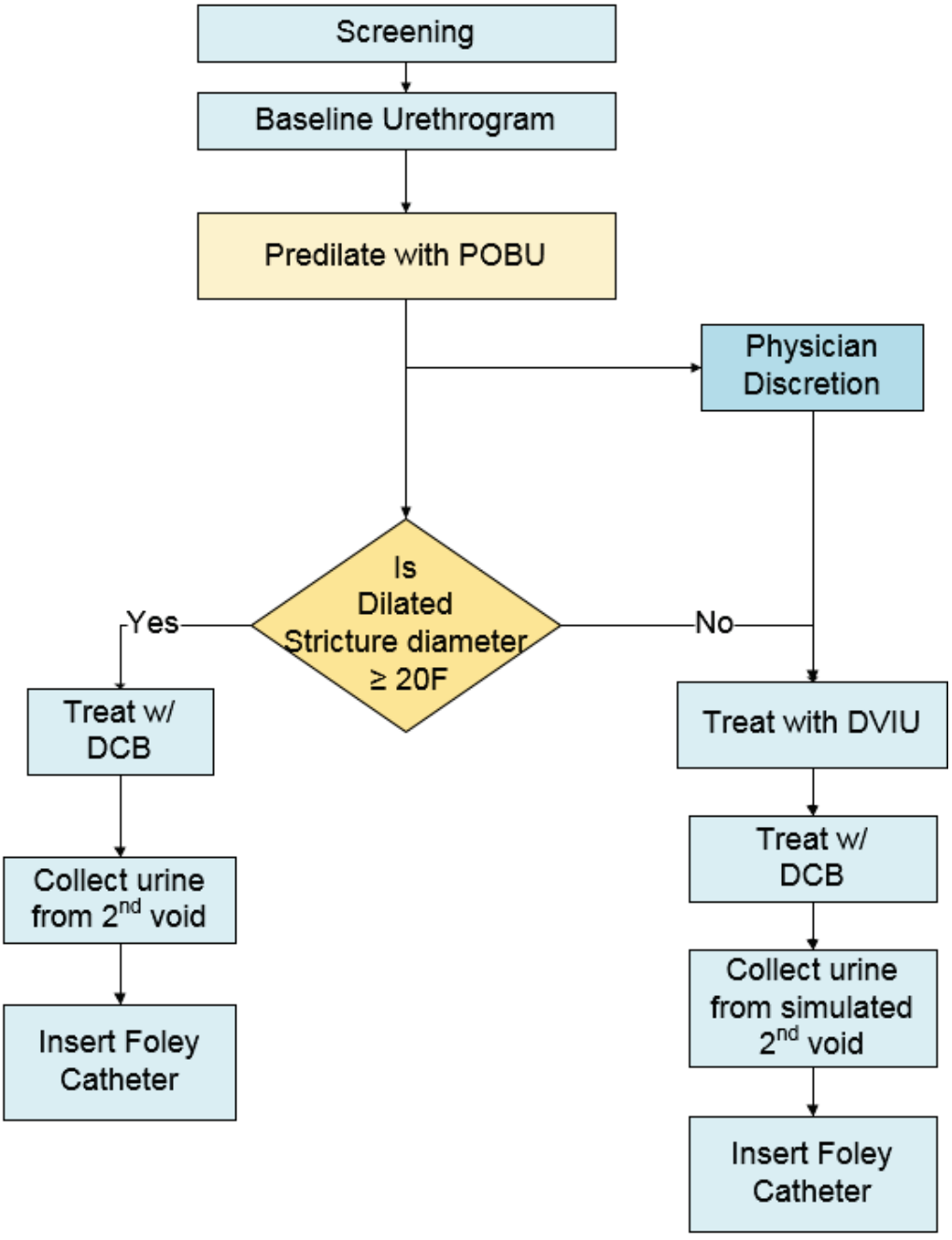


Figure 3-1: Study Treatment Flow Chart

3.3 Study Endpoints

3.3.1 Endpoint 1: Rate of Treatment Related Serious Complication

This safety endpoint is defined as a composite device related serious complications at 90 days. Device related is defined to include both device and procedure related.

- Device related formation of fistula
- Device related de novo severe urinary retention lasting > 14 consecutive days' post-treatment.
- Device related Unresolved de novo stress urinary incontinence (requiring >1 pad/day) at 90 days or earlier
- Urethra rupture or burst

3.3.2 Endpoint 2: Improvement in IPSS (International Prostate Symptoms Score)

3.3.3 Endpoint 3: Stricture Recurrence Rate

The definition of stricture recurrence is the urethra lumen being < 14 F with or without recurrence of symptoms at 6 months. The urethra caliber will be measured as follows:

- Passage of a flexible cystoscope to determine ≥ 16 Fr urethral caliber
- If the 16F flexible scope would not pass, then a 14 Fr flexible rubber catheter will be inserted through the treated section

Note: Obstruction symptoms due to BPH (Benign Prostatic Hyperplasia) will not be considered a stricture recurrence.

3.3.4 Endpoint 4: Improvement LUTS (Lower urinary tract symptoms) Voiding Construct (Mundy PROM) Score (Patient-reported outcome measure)

3.3.5 Endpoint 5: Change in IIEF (International Index of Erectile Function)

3.3.6 Endpoint 6: Repeat Treatment Rate

This is defined as repeat surgery or treatment for urethral stricture in the same location of the urethra.

3.3.7 Endpoint 7: Change in Qmax (Peak Flow Rate) at 3 and 6 months

Assessment of the maximum urinary flow rate during uroflowmetry. The test is only valid if the voided volume is greater than 125ml.

3.3.8 Endpoint 8: Paclitaxel content in blood, urine and semen

Measurements will be measured by an independent laboratory following GLP regulations.

3.3.9 Endpoint 9: Stress Urinary Incontinence at <90 days and >90 days

-

Cystoscope or catheter should not be passed through the treatment area unless medically indicated or physician suspect the patient's health is in jeopardy or treatment failure is suspected based on one or both of the criteria above. Obstructive symptoms due to other reasons (e.g. BPH, bladder neck constriction) other than stricture is not considered a treatment failure.

4 SUBJECT SELECTION

A subject is considered enrolled if:

- Meet all the inclusion criteria
- Does not meet ANY exclusion criteria
- Provided informed consent
- Introduced the investigational device

4.1 Inclusion Criteria

1. Male subjects ≥ 18 years' old
2. Visual confirmation of stricture via cystoscopy or urethrogram
3. Single lesion anterior urethral stricture or bladder neck contracture, less than or equal to 2.0 cm
4. One to three (1-3) prior diagnosis and treatment of the same stricture (including self-catheterization) including DVIU (Direct Vision Internal Urethrotomy), but no prior urethroplasty
5. Significant symptoms of stricture such as frequency of urination, dysuria, urgency, hematuria, slow flow, feeling of incomplete emptying, recurrent UTI's.
6. IPSS score of 13 or higher
7. Lumen diameter <12F by urethrogram
8. Able to complete validated questionnaire independently
9. Qmax <10 ml/sec

4.2 Exclusion Criteria

1. Strictures greater than 2.0 cm long.
2. Subjects that have more than 1 stricture.
3. Sensitivity to paclitaxel or on medication that may have negative interaction with paclitaxel
4. Subjects who have a suprapubic catheter and are unable to complete study required testing, such as uroflowmetry
5. Previous urethroplasty within the anterior urethra
6. Stricture due to bacterial urethritis or untreated gonorrhea
7. Stricture dilated or incised within the last 3 months
8. Presence of local adverse factors, including abnormal prostate making catheterization difficult, urethral false passage or fistula.
9. Presence of signs of obstructive voiding symptoms not directly attributable to the stricture such as BPH at the discretion of the clinical investigator
10. Previous radical prostatectomy
11. Previous pelvic radiation
12. Diagnosed kidney, bladder, urethral or ureteral stones or active stone passage in the past 6 months.
13. Diagnosed with chronic renal failure unless under hemodialysis or has a serum creatinine level greater than 2 mg/dL
14. Use of alpha blockers, beta blockers, OAB (Overactive Bladder) medication, anticonvulsants (drugs that prevent or reduce the severity and frequency of seizures), and antispasmodics where the dose is not stable. (Stable dose is defined as having the same medication and dose in the last six months.)
15. Use of Botox (onabotulinumtoxinA) in urinary system within the last 12 months

16. Presence of a penile implant, artificial urinary sphincter, or stent(s) in the urethra or prostate
17. Known neurogenic bladder, sphincter abnormalities, or poor detrusor muscle function
18. Diagnosed with Lichen Sclerosus, or previous hypospadias repair
19. History within the last 5 years of carcinoma of the bladder or prostate
20. 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 of randomization
21. Any cognitive or psychiatric condition that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affect the ability to complete the study quality of life questionnaires
22. Unwilling to use protected sex for ≥30 days post treatment
23. Inability to provide legally effective Informed Consent Form (ICF) and/or comply with all of the required follow-up requirements
24. Participation in other pre-market studies
25. Stricture due to balanitis xerotica obliterans (BXO)

4.3 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 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 institutional ethics committees (EC).

5 PHYSICIAN SELECTION

Physicians selected must have experience in performing cystoscopies, treating strictures endoscopically as well as urethral reconstruction and/or other male urological therapies. Selected physicians will be trained in the use of the Urotronic DCB prior to enrolling subjects. The primary investigator will ensure that only trained sub-investigators who satisfy the physician selection criteria can perform any part of 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.

6 STUDY PROCEDURES

6.1 Pre Screening, Screening, and Baseline

The site may pre-screen potential subjects by reviewing medical records to identify the study population. 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 treatment as possible and repeated if needed. A baseline urethrogram must be performed prior to enrollment. Any required procedures performed before obtaining informed consent as part of the standard of care may be used in lieu of the study tests as described in Table 6-1.

The following evaluations will be completed for all study candidates. Evaluations performed within the screening window may be acceptable. The required baseline evaluations prior to enrollment are shown below:

Table 6-1: Screening Evaluations Conditions

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
Medical history	Within 30 days	Evaluation is complete and adequately documented in report for assessment
Physical exam evaluation	Within 30 days	Evaluation is complete and adequately documented in report for assessment
Uroflowmetry[1] • Voided volume (must be ≥ 125 mL or test must be repeated for all the uroflow tests) • Voiding time • Peak flow rate (Qmax)[1] • Average flow rate	The uroflow reading must be within 30 days of treatment	Must be performed before cystoscopy or ≥14 days after cystoscopy and no evidence of UTI The uroflow method used in the second screening test must be the same as that used in the follow-up tests.
Post-void residual urine volume (PVR; may be measured by either ultrasound or catheterization but the same method must be used pre- and post-treatment)	Within 30 days of treatment	Must be performed before cystoscopy or ≥14 days after cystoscopy and no evidence of UTI The PVR method used during screening must be the same as that used in the follow-up tests.
Blood analysis • Complete blood cell count (CBC) • Blood urea nitrogen (BUN)	Within 30 days	

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
• Serum creatinine • Alanine aminotransferase (ALT) • Drug Analysis		
Urine analysis • Sugar • Protein • WBC/RBC • Bacteria • Drug analysis • UTI	Within 7 days	Must be negative for infection before enrolling
Urine culture for infection only if infection is suspected	Within 7 days	Must be negative for infection before enrolling
Semen collection	Within 30 days	Patients must abstain from ejaculation 48 hours prior to semen collection
Urethral Stricture Score (USS)	Within 30 days	None
Subject questionnaires • Mundy PROM • International Prostate Symptoms Score (IPSS) - Standard • International Index of Erectile Function (IIEF) • VAS Pain Scale	Within 30 days	Must have documented negative infection before enrolling and before taking the IPSS Mundy PROM at baseline
Screening flexible cystoscopy	Within 2 months prior to enrollment	Prior cystoscopy before enrollment is acceptable only if video is available for viewing
Screening urethrogram (recorded)	Within 30 days prior to enrollment	Prior urethrogram before enrollment is acceptable only if video is available for view
Current or prior (up to 6 months) medication consumption	Prior to enrollment	A list of current and prior medication is required to determine if the dose is stable.

6.2 Subject Enrollment

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

6.3 Concomitant Therapy

Therapy (medication and non-medication therapies) not restricted by a protocol requirement 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.

Standard dose of antibiotic is required to be administered before and after treatment.

6.4 DCB Treatment Study Procedure

The treatments for the study may be performed in a hospital or ambulatory surgical center. A summary of a typical procedure is described in this section. The treatment algorithm is schematically shown in Figure 6-1.

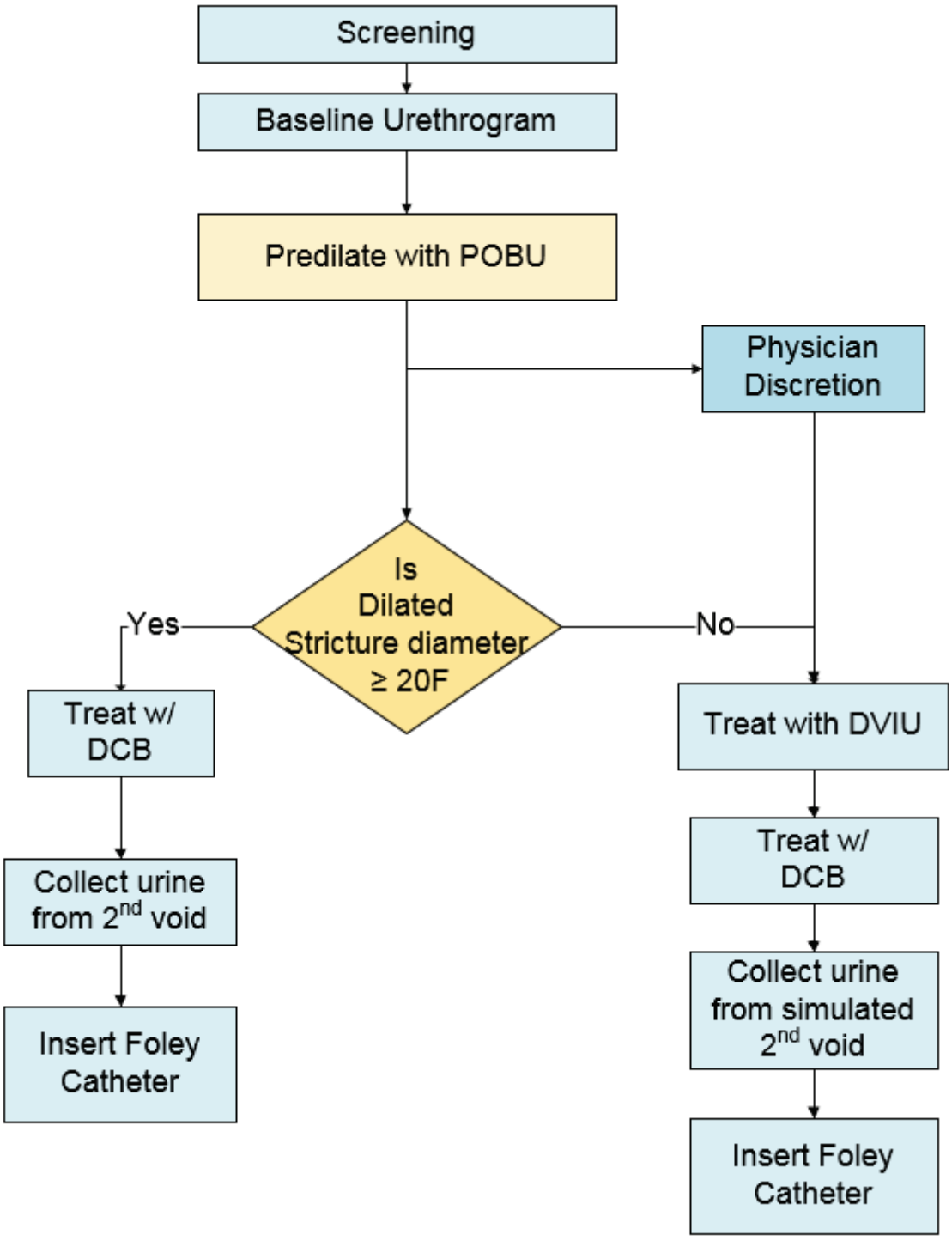


Figure 6-1: Treatment Algorithm

6.4.1 Peri Procedural Medication

General anesthetics is recommended for all patients. Recorded anesthesia used in the case report form.

A 5-day course of oral antibiotic is required to be administered prior to the procedure. If a urinary tract infection (UTI) is indicated, the patient must be treated until the infection is cured before the study procedure. Oral NSAID or low dose aspirin is also recommended to be given prior to the procedure.

6.4.2 DCB Treatment

The DCB should be prepared per the Instructions for Use (IFU). A summary is provided below. If the summary is different from the IFU, follow the instruction for the IFU.

Predilation

1. Perform a baseline urethrogram if one was not recorded within 7 days. RECORD the urethrogram.
2. Place the guidewire through the urethra with the tip of the guidewire in the bladder. Typically, this will be through the working channel of a cystoscope.
3. Track the selected predilation catheter over the guidewire with the aid of the cystoscope alongside the catheter.
4. Check the position of the balloon radiopaque markers are in the correct position using fluoroscopy.
5. Predilate the stricture with a standard uncoated balloon (POBU), plain old balloon urethroplasty). Do not exceed rated burst pressure of the balloon. If the stricture is not dilatable (*Dilatable is defined as stricture diameter post predilation increase by ≥ 20F by visual estimation or at physician discretio*n), the subject will be treated per DVIU prior to DCB treatment.
6. If DVIU is indicated (see Figure 6-1); perform DVIU in 3 positions (approximately: 12 o'clock, 5 o'clock and 7 o'clock).
7. Perform a urethrogram. If the lumen is <20F, perform predilation with an uncoated balloon. Record lumen size with urethrogram.

DCB Treatment

8. Ensure that the urethra is flushed with saline and fill the bladder with saline before introduction of the DCB.
9. Position the DCB across the predilated or DVIU treated stricture with the cystoscope proximal to the balloon (away from the bladder) to visualize the proper placement of the balloon across the stricture. Leave the balloon in position uninflated for a minimum of 1 minute prior to inflation.
10. Check that the balloon radiopaque markers are in the correct position using fluoroscopy.

11. Inflate the balloon with a 50/50 contrast solution using the Balloon Indeflator. Do not exceed rated burst pressure of the balloon. Maintain pressure for a minimum of 5 min.
12. RECORD the fluoroscopic image with the balloon inflated. Record the inflation pressure.
13. Remove the device(s).
14. Collect urine sample (2nd void):
    a. Ask subject to void or palpate the bladder to allow about 1 cup (100 – 150ml) of fluid to flow out of the urethra to flush any residual coating particles. This is recognized as the 1st void
    b. Then ask subject to void or palpate the bladder again, collect the urine sample for about 100 ml or any remaining residual fluid for analysis. This is recognized as the 2nd void.
15. Insert a 12-14 Fr Foley catheter (provided by the sponsor) for at least 5 days. Record the Foley catheter size and time of catheter removal.

6.4.3 Treatment Rules

- An increase of urethral caliber lumen to 20F or greater must be achieved by predilation to proceed to DCB treatment. If dilation failed to increase the lumen by 20F or greater, the subject will be treated with DVIU, followed with a DCB treatment. At the physician discretion, the patients may be enrolled directly into the DVIU group.
- The DCB balloon catheter must be inflated at the target stricture to the recommended pressure for a minimum of 5 minutes with saline/contrast.
- After dilation with DCB, no instrumentation can be passed through the stricture acutely with the exception of the Foley catheter (≤ 14F size) when medically needed.
- Use only the lubricious Foley catheter provided by the sponsor.

6.4.4 In-Hospital to Discharge

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are recommended together with the use of antibiotic.

Blood PK (Pharmacokinetics) Samples

For subjects (up to 30), who agreed to be part of the PK cohort, a total of 8 blood samples will be collected per subject, at the following time points. The first blood sample at baseline, then the next 6 blood samples (#2 - #7) will be drawn prior to discharge. The 8th blood sample will be drawn post discharge at the 5 days follow up visit. After June 5th, 2017, only the subjects who have DVIU, or have the 2nd study procedure (Retreatment), will be asked to participate in the PK test.

Time points of blood sample collection:

# of Samples	Time points	Approximate Compliance Window*
1.	Baseline	- 30 days of procedure
2.	0 hr	+ 25 min
3.	1 hr	+ 30 min
4.	3 hrs	± 1 hr
5.	5 hrs	± 1 hr
6.	10 hrs	± 2 hrs
7.	24 hrs	± 4 hrs
8.	5 days	± 1 day

The definition for "0 hour" is post-procedure soon after collecting the urine sample.

Sexual Activities

All subjects must be counseled about sexual activities post treatment as follows:

- All patients will be asked to ABSTAIN from ALL sexual activities including masturbation for 14 days
- 48 hours prior to semen collection, patients must abstain from ejaculation
- Use of condom or abstain from sex for the first 30 days after treatment. The time of protected sex may be extended by the physician depending on the drug test results in the semen.

6.5 Retreatment

6.5.1 Retreatment Rules

A subject may undergo a retreatment procedure at any point after the 3-month follow-up or before the 6-month follow-up visit, if the retreatment is recommended by the treating physician and meet one of the following criteria:

1. Treatment was not successful and subject still experienced retention and continue to meet the inclusion and exclusion criteria
2. Initial DCB treatment was abandoned or truncated due to discomfort, poor visibility or incorrect placement of DCB. In this instance, retreatment can be performed prior to the 3 months.
3. Subjects must continue to meet the initial inclusion/exclusion criteria to be eligible for retreatment.

All retreatment subjects will have the stricture predilated with DVIU prior to DCB treatment. Only one retreatment is allowed for each subject. The safety and effectiveness data collected post-retreatment will be pooled with the other subjects for analysis but the retreatment cohort data will also be summarized and provided separately. Retreated

subjects will be followed out to 5 year follow-up time points, starting from the retreatment time , under the same subject ID.

6.6 Scheduled Follow-up Evaluations

The following evaluations will be completed at each visit as indicated in Table 6-2. Subjects will be evaluated at baseline, immediately post-procedure, 5 days, 14 days, 30 days, 3 months, 6 months and 12 months' post-procedure.

Annual evaluation of the stricture treatment may be followed for up to 5 years post treatment.

Table 6-2: Scheduled Evaluations and Follow UP

	Baseline	Intra-Procedure	Pre-Discharge	5 days	14 days	30 days	3 Months	6 and 12 Months	Annually for up to 5 years	Unscheduled Visit
Compliance Window	-30 days	NA	NA	± 1 day	± 2 days	± 5 days	± 14 days	± 30 days	± 60 days	NA
Physical Examination	√				√	√	√	√	√	√
Medication Usage Review	√	√	√	√	√	√	√	√		√
Antibiotic	√ (pre-procedure)		√							
Blood analysis (Complete blood cell count (CBC), Blood urea nitrogen (BUN), Serum creatinine)	√		√	√						
Alanine aminotransferase (ALT)	√			√						
Urine Analysis (sugar, protein, WBC/RBC, Bacteria (UTI))	√ Within 7 days of procedure				√	√	√			√
Urine collection (drug analysis)	√		√ (2^{nd} Void)	√	√	√				

	Baseline	Intra-Procedure	Pre-Discharge	5 days	14 days	30 days	3 Months	6 and 12 Months	Annually for up to 5 years	Unscheduled Visit
Compliance Window	-30 days	NA	NA	± 1 day	± 2 days	± 5 days	± 14 days	± 30 days	± 60 days	NA
Blood collection (drug analysis)	√ [1]		√ [1] (multiple samples in 24 hrs)	√ [1]						
Review Protected Sexual Activities			√	√	√	√	√ [3]	√ [3] (6 months only)		
Semen Evaluation	√ (sperm quality)				√ (sperm and drug)	√ (sperm and drug)		√ (6 months for sperm only)		
USS	√									
Mundy PROM	√				√	√	√	√	√	√
IPSS, IIEF	√				√	√	√	√	√	√
VAS Pain score	√		√	√	√	√				
Qmax	√				√	√	√	√	√	√
PVR	√				√	√	√	√	√	√
Urethrogram	√ Record	√ [4] Record					√ Record	√ Record		

	Baseline	Intra-Procedure	Pre-Discharge	5 days	14 days	30 days	3 Months	6 and 12 Months	Annually for up to 5 years	Unscheduled Visit
Compliance Window	-30 days	NA	NA	± 1 day	± 2 days	± 5 days	± 14 days	± 30 days	± 60 days	NA
Cystoscopy	√ Record							√ Record (16F cystoscope)		√ Record
14F Rubber catheter urethral Lumen evaluation								√ (If 16F scope failed to pass)		
Subject Satisfaction Questionnaire							√	√		
AE Review	√		√	√ [2]	√	√	√	√	√	√

Note

1 – For the PK test, a total of 8 blood samples will be collected /patient. It requires patients to stay in the hospital overnight for blood draws at 0 , 1, 3, 5, 10, 24 hrs post-procedurely. The blood draws at baseline and 5 days follow-up will be done accordingly, but no hospital stay is required.

2 – Pain /discomfort after the procedure is common and to be expected. Steps can be taken to minimize or eliminate pain /discomfort. It is at physician's discretion, whether the pain /discomfort is an adverse event, or a normal healing process.

3 – Review may be eliminated depending on the results of drug analysis from first 5 subjects. If so, a notice will be given to the study sites by Sponsor.

4 – Recorded Fluroscopy/urethrogram required before any intervention, during predil, post dil, during DCB, after DCB (fluoroscopy only)

6.7 Unscheduled Follow-up Visits

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

6.8 Premature Exit or Alternate Treatments

Subjects that opt for alternate treatments for stricture within 3 months of treatment will be considered to have failed the treatment. Treatment for BPH symptoms are not considered a failure.

6.9 Multiple IPSS and Mundy PROM Responses

If multiple responses to the same questionnaires are available for each visit window, the average value of the scores will be used unless there are valid scientific reasons to exclude one of the readings.

6.10 Lost to Follow-up

If a subject fails to comply with follow-up evaluations, 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 evaluations, but is present at the subsequent follow-up, the subject can be readmitted into the study and queried retrospectively for basic information (e.g., AEs); however, the missed evaluation must be documented on a Protocol Deviation CRF. The IPSS and other questionnaires will be collected prospectively only.

6.11 Subject Withdrawal from Study

6.11.1 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.

6.11.2 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 exclusion criteria. However, these subjects will continue to be followed per the requirements of their particular arm unless instructed otherwise by the IRB/EC. The major exclusion criteria that would cause the withdrawal of the subjects' data are:

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

The decision to exclude the subject's data from analysis will be documented in the CRF.

6.11.3 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.

6.12 End of Study

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

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

7 SUBJECT EVALUATION DESCRIPTION

7.1 Subject Questionnaires

All questionnaires are self-administered and will be completed at baseline and at required follow-up visit. 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.

7.1.1 USS Score

The USS is a numerical score based on five components of anterior urethral stricture disease that help dictate operative decision-making: (1) urethral stricture etiology; (2) t otal number of strictures; (3) retention (luminal obliteration); (4) anatomic location; and (5) length. The USS describes the essential factors in determining surgical treatment selection for urethral stricture disease. The USS is a concise, easily applicable instrument that delineates the clinically significant features of urethral strictures.

7.1.2 Mundy PROM

This is a validated patient-reported outcome measure (PROM) for anterior urethral stricture surgery constructed from existing questionnaire. This PROM defined a succinct, practical, and psychometrically robust PROM designed specifically to quantify changes in voiding

symptoms and HRQoL following urethral stricture surgery and for this study will be referred to as the Mundy PROM for convenience. Q1 to Q6 are based on ICIQ-MLUTS voiding construct and will be referred to as Mundy Prom Voiding Construct.

7.1.3 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. However, the symptoms of BPH and urinary stricture are very similar and has been used with strictures.

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). Although there are no standard recommendations for grading patients with mild, moderate, or severe symptoms, patients can be tentatively classified 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, except the one week follow-up.

7.1.4 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 one week follow-up visits and if indicated, at unscheduled visits.

7.1.5 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.

7.1.6 Subject Pain Questionnaire

Pre and post-procedure pain will be evaluated using a standardized pain questionnaire.

7.2 Uroflowmetry

Subjects will be asked to hydrate and refrain from voiding for two hours. 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 case report forms 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 (≥ 5ml/sec to < 15 ml/sec to qualify) averaged over a 2 second interval
- Average flow rate
- Voiding time

7.2.1 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.

7.2.2 Post Void Residual Urine Volume

Following uroflowmetry, residual urine volume in the bladder shall be assessed by bladder scanner ultrasound.

7.3 Flexible Cystoscopy

A screening flexible cystoscopy may be performed to confirm the presence of stricture and to estimate the stricture conditions (length and size) prior to enrollment in the study. The size and length is to be estimated without crossing the stricture at screening. A post treatment flexible cystoscopy will be performed at the 6-month follow-up and subsequent follow up when cystoscopy is warranted.

7.4 Urethrogram

A retrograde urethrogram (RUG) is taken to diagnose the stricture, ensure the stricture is dilatable post predilation, and to assess stricture recurrence at follow-ups. The general procedure steps are outlined below.

- Position the patient and fluoroscope equipment so a lateral view, with the urethra in a single plane relative to the image is obtained.
- Retract the foreskin and clean the tip of penis with betadine or antiseptic solution.
- Liberally administer lidocaine jelly over the outside tip and shaft of a short 8F introducer sheath.
- Place the introducer sheath into the tip of the penis. Then place a markerwire into the introducer sheath down into the urethra. Ensure the markers are visible in the fluoroscopic image. This is used for urethogram image distance calibration.
- Attach a 50/50 saline/contrast loaded syringe to the introducer sheath.
- Simultaneously inject the contrast and start a cine to capture the urethrogram.

Ideal image frames used for analysis demonstrate the entire length of the urethra with contrast beginning to fill the bladder.

7.5 Rubber Catheter

Rubber catheters with known diameters may be used to estimate the status of the stricture.

8 STATISTICAL CONSIDERATIONS

8.1 Statistical Analyses

The data from the study will be tabulated using descriptive analyses.

Descriptive analyses of all AEs and urinary symptoms will be provided in the report. In addition, the report will include tabulated results of study deviations and device malfunctions.

Details of the statistical analysis will be provided in the statistical analysis plan (SAP).

9 DEFINITION OF ADVERSE EVENT(S)

For purposes of this study, an adverse event (AE) is defined as any adverse change (i.e., *de novo* or preexisting condition) from the subject's baseline medical condition(s) occurring during the course of the study. For the purpose of AE documentation, the start of the course of the study is defined as any time after the treatment has been initiated. All AE's will be recorded in the CRF whether considered procedure-related or not, and will be classified as described in Section 9.5.

Pre-existing conditions will not be reported as an AE unless there is an adverse change in that condition. Any AE which resolved and then recurred will be reported as a separate AE.

An AE may be volunteered spontaneously by the subject or discovered as a result of questioning or physical examination by an investigator or study staff.

9.1 Treatment Related Symptoms

The Urotronic DCB procedure is designed to treat strictures. Subjects to be treated have moderate to severe LUTS prior to treatment. These symptoms are expected to continue and may even worsen slightly prior to improvement as part of the healing process. All reported LUTS will be documented in the CRF. Other expected acute but transient worsening of symptoms from the treatment are dysuria, frequency of urination, urgency of urination, urge incontinence, hematuria, slowing of the urinary stream and acute retention as the tissue heals.

Worsening or de novo LUTS, dysuria or non-obstructive hematuria that occur and resolve within 14 days of treatment that do not require intervention (other than catheterization,

prophylactic antibiotic, anti-inflammatory medication, and pain medication) will not be considered an AE as these are expected and part of the healing process. However, all treatment and related symptoms will be recorded in the CRF.

Intervention as it relates to hematuria includes but is not limited to, hospitalization, the need to irrigate the bladder and urethra, or the need for transfusion therapy.

Common urinary symptoms will be considered an AE if any of the following occur:

a. Worsening or de novo LUTS requiring intervention or persisting beyond 14 days post treatment;
b. Worsening or de novo LUTS requiring hospitalization or intervention other than the use of catheterization, one standard course of antibiotic, anti-inflammatory and/or pain medication;
c. Hematuria that requires irrigation or is obstructive;
d. Urinary tract infection defined as $>10^5$ CFU of a single organism plus symptoms localized to bladder.
e. Urinary retention that did not resolve within 10 days of treatment; or
f. If de novo LUTS recurs after the same symptom is resolved and is considered clinically significant.

9.2 Urinary Retention and Catheterization

Acute urinary retention that resolves within 10 days will not be considered an AE. However, any catheterizations or cystoscopies will be recorded in the CRF. Resolution is defined as a removal of the catheter without the need to reinsert it or use of intermittent self-catheterization.

While catheterization in and of itself is not an AE, the *reason* for catheterization must be evaluated for purposes of determining an AE.

9.3 Urinary Retention Definition

Urinary retention, also known as ischuria, is a total lack of ability to urinate. It is sometimes referred to as acute urinary retention and typically has to be treated with a catheter or stent to avoid serious complications of the bladder and/or kidney.

9.4 Obstructive LUTS

Obstructive LUTS has some symptoms similar to Urinary Retention. Obstructive LUTS is usually a chronic condition and is sometimes referred to as chronic urinary retention. Symptoms of obstructive LUTS are:

- Poor stream
- Hesitancy
- Terminal dribbling
- Incomplete voiding

- Overflow incontinence (occurs in chronic retention)

9.5 Coding or Classification of AEs

Adverse events should be classified according to their underlying cause, if known (e.g., fever resulting from infection should be reported as "infection"). Symptoms related to a diagnosis should not be reported as separate AEs. In the above example, fever is a symptom caused by infection and should be reported as infection only.

Concomitant AEs that are unrelated (in the clinician's judgment) should be reported as separate events.

AE determination is based on three levels of evidence:

Level 1 – final diagnosis

Level 2 – signs

Level 3 – symptoms

Every effort should be made to collect Level 1 evidence of any AE. If an AE has all three levels of evidence, the AE should be reported only once at the highest level of severity, which is the final diagnosis (Level 1). A single AE should not be reported as multiple AEs based on separate symptoms and signs.

In cases where a diagnosis is not possible, AE determination should be based on the next highest level of evidence (i.e., Level 2: signs), followed by symptoms (Level 3), if symptoms are all that are available to the investigator.

A corrective action (e.g. catheterization) itself is not an AE but the reason of the catheterization may be an AE. The AE determination always should be based on the reason that a corrective action was taken. Note: there may be multiple signs or symptoms representing only one AE. Figure 9-1 below is an AE determination and outcome flowchart.

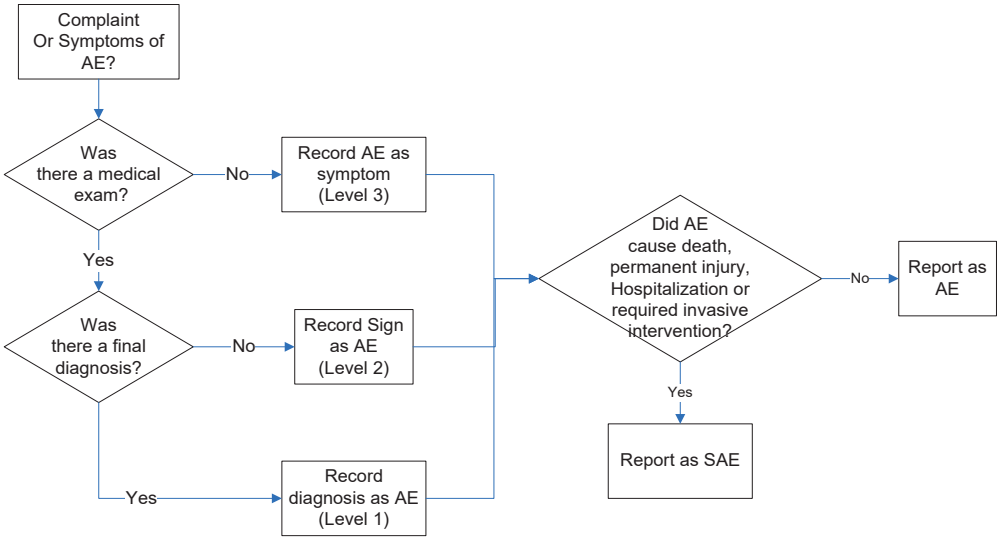


Figure 9-1: AE Determination and Outcome Flowchart

Example 1 (Diagnosis): prostatitis often has dysuria, urinary frequency, nocturia, difficult urination, pain in the groin, pelvic area or genitals, painful ejaculation, and sometimes, flu-like symptoms such as fever and chills. If the diagnosis can be established, prostatitis should be the AE, not the other symptoms. The other symptoms may be listed with the AE.

Example 2 (Diagnosis): Urinary tract infection (UTI) often has dysuria, urinary frequency, urinary urgency, and hematuria. If the diagnosis of UTI can be established, the AE should be classified as an infection with sub-classification of UTI. The symptoms may be listed with the AE.

Example 3 (Sign): Hematuria may lead to other symptoms, such as dysuria, pain in flank and back, in addition to blood in the urine. A blood clot may obstruct the urethra and lead to urinary retention. A disease diagnosis is preferred but a diagnosis may not be possible. In this case, hematuria (with clot retention) should be the AE classification/category, not the other symptoms.

9.6 Potential Anticipated Adverse Events

Potential anticipated adverse events are those that may occur in association with a stricture treatment or procedure, include those AEs listed below or reported in the literature associated with surgical or minimally invasive stricture procedures:

Surgical and Procedural Risks

- Adverse reaction to the drug (paclitaxel) coating

Paclitaxel has been reported to prevent proliferation (growth of certain cells in the body). In this study, the purpose of using paclitaxel on the device is to help prevent or reduce restenosis (stricture reoccurring). However, the risks of exposure to Paclitaxel include:

- Chromosomal abnormalities and the risk of cancer
- Fetal harm when a pregnant woman is exposed
- Anaphylaxis (allergic reaction) and hypersensitivity reaction with paclitaxel intravenous infusion
- Delayed healing of the wound in urethra due to the procedure
- Potential effect on the liver and kidneys is unknown and have not been studied

The amount of the paclitaxel delivered is much lower than a single dose of chemotherapy provided to cancer patients and the drug appears to remain relatively localized.

- Sepsis and infection
- Fever
- Perforation of urethra
- Perforation of adjacent organs including the rectum, bladder and GI tract
- Urinary symptoms and adverse events including:
  - Dysuria
  - Frequency
  - Urgency
  - Nocturia
  - Acute urinary retention
  - Incontinence
  - Sensation of not emptying bladder completely
  - Urethritis
  - Irritative urinary symptom
  - Urethral injury causing false passage or adhesion
  - Urinary clot retention
  - Chronic pain in the pelvic area
  - Bladder spasm
  - Urethrorrhagia or Hematuria with or without clot in urethra
  - Discharge or cloudy urine
  - Discharge of tissue material during urination
  - Scarring of the urethral system
  - Urinary tract infection
- Abscess (prostatic, bladder, scrotal)
- Bladder problems or damage (reduced bladder sensation, spasms, bladder neck contracture, bladder neck stenosis)
- Bladder perforation or rupture
- Damage to the urethral system
- Worsening of stricture or de novo stricture

- Seroma
- Kidney compromise or failure
- Reproductive system disturbances such as infertility and miscarriages
- Prostate abnormalities and damage

Other Pelvic Health Risks

- Rectal incontinence
- Rectal damage
- Rectal stenosis
- Rectal, perineal findings
- Anal irritation
- Elevated PSA
- Nerve damage
- Weakness or numbness
- Abdominal or low back pain
- Flu-like symptoms
- Hematospermia
- Epididymitis
- Bowel irritation
- Erectile dysfunction
- Retrograde ejaculation or ejaculatory dysfunction
- Pressure sensation
- Prostatitis

Other potential non-pelvic anticipated adverse events that may occur in this subject population are:

- Blood pressure change during therapy
- Arrhythmia
- Flank pain
- Blood loss (> 500 ml)
- Adverse reaction to medication and anesthesia as listed in the labeling
- Low blood pressure (hypotension)
- High blood pressure (hypertension)
- Fainting, dizziness, or blurred vision (vasovagal reaction, syncope)
- Allergic reaction
- Fatigue
- Dyspnea
- Confusion
- Memory loss
- Swelling or bruising (edema, hematoma)
- Aneurysm – thoracic and cranial
- Low back pain

- Pneumonia
- Collapsed lung
- Pulmonary embolism
- Pneumothorax
- Upper respiratory disease
- Cough
- Sore throat
- Apnea
- Coughing up blood (hemoptysis)
- Choking (aspiration)
- Venous thrombosis
- Myocardial infarction, angina, ischemia
- Cardiac arrhythmia
- Stroke or transient ischemic attack
- Brain damage
- Headache
- Depression
- Perforation of or damage to the gastrointestinal tract
- Abdominal pain
- Constipation
- Nausea or vomiting
- Adverse reaction to medication

9.7 Definition of Serious Adverse Event(s)

An adverse event is considered to be a serious adverse event (SAE) if it resulted, or could result in, if not mitigated in:

- Death
- Is life-threatening
- Requires the subject to be hospitalized or prolongs an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is considered an important medical event

Important medical events that may not meet one of the above definitions could be considered SAEs if they jeopardize the health of the subject or require surgical intervention to prevent one of the outcomes listed above. An SAE may or may not be related to the study procedure.

9.8 Unanticipated Adverse Device EFFECT(s) (UADE)

An unanticipated adverse device effect (UADE) is any serious adverse effect on the health or safety of a subject, any life-threatening problem or death caused by, or associated with a device, if such effect, problem, or death was not previously identified in nature, severity, or

degree of incidence in the investigational plan (e.g., ICF, Study Protocol, Instructions for Use (IFU), publications, etc.), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If an unanticipated adverse effect associated with the investigational device occurs, the investigator shall notify the Sponsor and the IRB/EC as soon as possible.

The Sponsor will investigate the event and notify the authorities and IRB/EC and all other participating IRBs/EC and investigators. Should the Sponsor determine that an unanticipated adverse effect presents an unreasonable risk to all participating subjects, the Sponsor will suspend the clinical investigation and notify all participating investigators, IRBs/EC, country regulatory bodies.

9.9 Reporting of all Adverse Events

The signs, symptoms and sequelae of an underlying AE should not be reported as separate AEs.

All AEs must be recorded on a CRF. All AEs also must be described by (a) duration (start and resolution dates); (b) adjudicated for severity; (c) relationship to the study device; (d) action taken to resolve the event; (e) outcome of the event; and (f) whether or not such event is considered to have been serious. Additional information, such as procedural notes, treatment notes, or a signed clinical summary, may be required as supporting documentation for the reported AE.

During the study, all deaths must be reported to the Sponsor within the period outlined in Table 12-1. All deaths also should also be reported on the End of Study CRF. A copy of the subject's death records, medical records for the events that led to the subject's death, and a death certificate (if available) should be provided.

9.10 Relationship of AEs to the Device

A description of how an AE relates to the study procedure will be reported on the Adverse Event CRF and be determined by the Investigator using the following definitions:

- ***Definite*:** The AE follows a reasonable temporal sequence from the time of the index procedure, which includes AEs that occur during the index procedure or during the follow-up period.
- ***Probable***: The AE follows a reasonable temporal sequence from the time of the index procedure, and the possibility can be excluded that factors other than the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment caused the AE.
- ***Possible***: The AE follows a reasonable temporal sequence from the time of the index procedure and the possibility of index procedure involvement cannot be excluded.

However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.

- ***Unlikely***: The AE has an improbable temporal sequence from the time of the index procedure, or such AE can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.
- ***Not related***: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

Those SAEs that are possibly related to the device, the procedure, or the disease state being treated will be reviewed and adjudicated by the sponsor.

9.11 Device Failures, Malfunctions and Near Incidents

Device failures or malfunctions will be reported to the sponsor by the clinical sites. If the failure or malfunction results in negative clinical sequelae, the event shall be reported to the Sponsor within two (2) working days after the Investigator becomes aware of the device-related adverse event and reported to the IRB/EC (if required) within the IRB/EC required timeframe. The malfunctioning investigational device involved in the incident should be returned to the Sponsor for evaluation.

10 TRAINING

The Sponsor will be responsible for training of appropriate clinical site study personnel. All physicians proctored by the Sponsor, as well as other trained physicians, must sign the site Proctoring Form in connection with this study. 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.

11 DATA MANAGEMENT

11.1 Subject Identification

Subjects that successfully pass the screening tests and wish to participate in the study will be assigned a unique identification code (ID) using the format “XX-YYY” where:

XX = Institution Number, assigned by the Sponsor to each study site

YYY = Enrollment Number, assigned by the institution as each subject is enrolled in the study

In addition to the ID, each subject's initials will be used as an identifier included on documentation submitted to the Sponsor.

1.1 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

12 STUDY RESPONSIBILITIES AND MANAGEMENT

12.1 Investigator Responsibilities

Each investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, EC/IRB 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/IRB roster (or IRB registration number from the Office of Human Research Protection)
- EC/IRB 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 above functions to an associate or Co or Sub-Investigator, or a trained Study Coordinator; however, the 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/IRB and the Sponsor.

12.2 Subject Enrollment Process

All study candidates, after pre-procedure screening, must appropriately consent to participate in the study, as administrated by qualified study site personnel using an EC/IRB and Sponsor-approved informed consent form (ICF) prior to beginning any aspect of the study procedure or tests that are not standard of care for the site. Investigational sites will be required to document the consent process within each enrolled subjects medical record. Administering the questionnaires can be done prior to signing the ICF.

Only subjects who meet the inclusion/exclusion criteria, who signed the study enrollment informed consent will be considered enrolled in the study.

Timely communication by each site is critical to avoid over enrolling when the enrollment is close to the end of each phase. When enrollment is close to the end of each phase, the following procedures will be implemented:

- Before the subject signs the study ICF, the Study Coordinator must confirm the availability of an enrollment slot. A phone call to the Sponsor or Data Coordinating Center is the preferred method.
- Immediately after the procedure, the Study Coordinator must inform (phone call or fax or e-mail) the Sponsor or Data Coordinating Center to confirm the subject's eligibility and the completion of the procedure. A phone call to the Sponsor is the preferred method.

12.3 Ethics Committee (EC) / Institutional Review Board (IRB)

Investigators must submit the study protocol to their respective Ethics Committee (EC) and or Institutional Review Board (IRB) and obtain the EC's/IRB'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/IRB, such as regular reporting, study timing, etc. Investigators will provide the Sponsor or its designee with copies of such approvals and reports.

12.4 Informed Consent Form (ICF)

The Sponsor will provide a template informed consent form (ICF) to each study site for EC/IRB 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/IRB.

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.

12.5 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), and 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 in the appropriate spaces provided using his/her electronic signature.

12.6 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;
- IRB/EC approval letter(s);
- Signed ICF;
- 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 and serial numbers 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.

12.7 Reports

Table 12-1 lists those reports that are the investigator's responsibility to deliver to the Sponsor. Each study investigator must follow the EC/IRB reporting requirements for their respective site. If applicable regulations or EC/IRB requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 12-1: Reports Required from Investigators to Sponsor

Type of Report	Prepared by PI for	Notification Time Frame
UADE	Sponsor, EC/IRB	Within 10 working days of knowledge
Death	Sponsor, EC/IRB	Written reports (e.g., via e-mail) within 48 hours
SAE	Sponsor EC/IRB, if required	Within 10 working days of knowledge Per EC/IRB requirement
Device malfunction with clinical sequelae	Sponsor EC/IRB, if required	Within 48 hours via written communication. Return the device to sponsor within 48 hours.
Serious protocol deviations (e.g., ICF not obtained, to protect the life or physical well-being of a subject in an emergency)	Sponsor EC/IRB, if required	Within 5 working days of knowledge Per EC/IRB requirement
Withdrawal of EC/IRB approval	Sponsor	Within 5 working days of knowledge

Type of Report	Prepared by PI for	Notification Time Frame
Progress report	Sponsor, EC/IRB	As required by EC/IRB
Final report	Sponsor, EC/IRB	Within 3 months of study completion or termination
Note: Each IRB/EC may require more stringent reporting requirements than those listed in this table.		

12.8 Sponsor Responsibilities

Urotronic, Inc. is the Sponsor of this study. The Sponsors 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.

12.8.1 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., urethrogram).

12.8.2 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/IRB 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/IRB prior to implementation. Following approval, any Investigational Protocol amendment must be distributed to all protocol recipients at the site.

12.8.3 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/IRB 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.). An Investigator must notify the Sponsor and the reviewing EC/IRB 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.

12.8.4 Protocol Deviation Notification/Approval to EC/IRB/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).

These types of deviations initiated by the clinical investigator must be reviewed and approved by the EC/IRB and the sponsor prior to implementation. This type of deviation can be used for historical data that is out of window (ie) 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.

12.8.5 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.

12.8.6 Device Accountability

The DCB allocated for investigational site use will be stored in a secured area until use. Each site will be responsible for tracking the receipt and disposition of all investigational Devices. All unused DCB Devices must be returned to the Sponsor at the end of the study.

13 STUDY ADMINISTRATION

13.1 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/IRB 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. All study monitors will be required to follow the Sponsor's monitoring plan and monitoring standard operating procedures (SOPs).

The study monitoring will be done by the following Sponsor representative:

13.1.1 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. It is anticipated each site will be monitored at least once upon the completion of the 3-month follow-up visits for all enrolled subjects at the study site. Monitors will require direct access to subjects' medical records pertinent to the study (and study inclusion criteria), study management documents, regulatory documents and Subject Informed Consent documents, as well as other potential applicable records not listed here.

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/IRB-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 IRB-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.

13.1.2 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/IRB. 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.)

14 STUDY CONTACT

14.1 Study Principal Investigator

14.2 Sponsor

14.3 Monitor and Data Management

15 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 efficacy will be provided to the EC/IRB as a supplemental application.

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

16 GLOSSARY OF ABBREVIATION

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
BPH	Benign Prostatic Hyperplasia
BUN	Blood urea nitrogen
CBC	Complete blood cell count
CFU	Colony Forming Unit
CIP	Clinical Investigation Plan
CRF	Case Report Form
DCB	Drug Coated Balloon
DES	Drug-eluting stent
DVIU	Direct Vision Internal Urethrotomy
EC/IRB	Ethics Committee / Institutional Review Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ID	Identification code
IFU	Instructions for Use
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptoms Score
LUTS	Lower urinary tract symptoms
NSAID	Nonsteroidal anti-inflammatory drug
OAB	Overactive Bladder
PROM	Patient-reported outcome measure
PSA	Prostate Specific Antigen
PVR	Post Void Residual Urine Volum
Qmax	Peak Flow Rate Measurement
RUG	Retrograde Urethrogram

SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TRUS	Prostate ultrasound or transrectal ultrasound
UADE	Unanticipated Adverse Device EFFECT(s)
USS Score	Urethral Stricture Score
UTI	Urinary Tract Infection

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