Prostatic **U**rethral **L**ift in **S**ubjects with **A**cute Urinary **R**etention Study (PULSAR)

Study Protocol

Clinical Protocol Number : CP00004 Revision D

14-December-2018

Sponsored by:

NeoTract®, Inc.

4473 Willow Road, Suite 100

Pleasanton, CA 94588

UroLift® System Registration # 252.1059 (NSAI)

UroLift® System CE Mark Approved: 3 June 2010

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INVESTIGATOR SIGNATURE PAGE

Trial Title	**P**rostatic **U**rethral **L**ift in **S**ubjects with **A**cute Urinary **R**etention Study (PULSAR)
Device	NeoTract® UroLift® System With commercial license
Protocol Number Version	CP00004, Revision D
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Trial Sponsor	NeoTract, Inc.

Investigator Acknowledgement Signature:

I,_____, and I, _____at
(name of principal investigator) (name of co-principal investigator)

the_____,
(name of hospital)

The undersigned, attest that we have read and understood this Protocol specified above and agree on its content and to abide by the above mentioned version and any subsequent amendments during my participation in the evaluation. We agree to perform and conduct the study as described in the protocol and in accordance with the relevant parts of the ICH Guidelines for GCP, the ISO 14155, the Declaration of Helsinki, and the pertinent individual country laws/regulations.

_____ _____
Principal Investigator Signature Date

_____ _____
Co-Principal Investigator Signature Date

Review by Head of Medical Affairs:

I have reviewed the contents of this PULSAR protocol CP00004 Revision D, and the Informed Consent Forms for the prospective and retrospective study arms in conjunction with Risk Management document RSK00003 Rev N. The expected potential benefits of participation in the PULSAR study outweigh the expected potential risks.

_____ _____
Jacqueline Welch M.D, Ph.D. Date

Medical Affairs

Approval by Head of Clinical Affairs:

_____ _____
Monica Ransom Date

Director, Clinical Affairs

1 Protocol Summary

Study Title	Prostatic Urethral Lift in Subjects with Acute Urinary Retention Study (PULSAR)
Study Objectives	Assess feasibility and safety of the Prostatic Urethra Lift (PUL) procedure in patients with acute urinary retention secondary to BPH. Research methodology will also be evaluated for larger, randomised study.
Study Design	Multi-centre, prospective evaluation of PUL and retrospective review of invasive surgery as potential comparator.
Sample Size	Up to 55 subjects treated with PUL. Retrospective chart review will include BPH patients that presented with AR and went on to de novo invasive surgery from June 1, 2015 to December 31, 2015.
Subject Population	Males over the age of 50 diagnosed with symptomatic benign prostatic hyperplasia (BPH) and ongoing acute urinary retention after failed TWOC.
Number of Centres (Sites)	Up to six centres in the United Kingdom.
Clinical Indication	The UroLift System is indicated for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men 50 years of age or older.
Primary Study Assessment	Successful post-procedure voiding trial without catheter (2-4 days).
Safety Assessment	Rate of serious adverse events (SAEs) related to BPH intervention through 3 months.
Additional Assessments	1. Need for further clean intermittent self-catheterisation (CISC) 2. Urinary symptoms, post void residual (PVR) and peak flow rate over follow-up 3. Subjects free from urinary retention through 1 month, 6 weeks, 3, 6 and 12 months 4. Subjects free from alternative surgical procedure for BPH through 12 months 5. Duration of catheter prior to treatment and in follow-up between prospective (PUL) and retrospective (TURP/HoLEP) 6. Rate of AEs in prospective PUL and retrospective TURP/HoLEP 7. Assess enrolment rate, willingness of patients to enrol, inclusion criteria, and appropriateness of endpoint
Follow-up Evaluations	Post-procedure, 6 weeks, 3 months, 6 months (remote), 12 months
Anticipated Study Duration	
First patient in (FPI)	15-April-2018
Last patient in (LPI)	31-December-2018
Endpoint analysis	28-February-2019
Study close	01-April-2020

2 Study Contacts

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3 Abbreviations and Definitions

Table 1 Abbreviations

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
AR	Acute urinary retention
AUR	Acute urinary retention
BPH	Benign Prostate Hyperplasia
BPH II	Benign Prostatic Hyperplasia Impact Index
CAPA	Corrective and Preventative Action
CEC	Clinical Events Committee
CI	Confidence Interval
CIP	Clinical Investigation Plan – Study Protocol
eCRF	Electronic Case Report Form
CT	Capsular Tab
DRE	Digital Rectal Exam
EC	Ethics Committee
EDC	Electronic Data Capture (system)
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
GCP	Good Clinical Practices
GU	Genitourinary
HoLEP	Holmium Laser Enucleation of the prostate, alternative to TURP
HRA	Health Research Authority
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IFU	Instructions for Use
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
IR	Independent Reviewer
ISI	Incontinence Severity Index
ITT	Intention-to-Treat
L.I.F.T.	Luminal Improvement Following Prostatic Tissue Approximation for the Treatment of Lower Urinary Tract Symptoms
LUTS	Lower Urinary Tract Symptom
MHRA	Medicines and Healthcare Products Regulatory Agency

MI	Multiple Imputation
MIST	Minimally Invasive Surgical Therapies
OUS	Outside U.S.
PET	Polyethylene Terephthalate
PP	Per Protocol
PRN	As needed
PSA	Prostate-Specific Antigen
PUL	Prostatic UroLift Procedure- procedure using the UroLift System
PVP	Photoselective vaporisation of the prostate by laser, alternative to TURP
PVR	Post Void Residual
Qmax	Peak Flow Rate
QoL	Quality of Life
R&D	Research & Development
Rx	Prescription Only
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
SHIM	Sexual Health Inventory for Men
TBD	To Be Determined
TRUS	Transrectal Ultrasound
TWOC	Trial to void without catheter
TURP	Transurethral Resection of the Prostate
UA	Urinalysis
U.S.	United States
US	Ultrasound
VAS	Visual Analog Scale

Table 2 Definitions

Adverse event (AE)	An adverse event (AE) is defined as any undesirable medical occurrence in a clinical trial subject, whether it is considered to be related to the device or not, that includes a clinical sign, symptom, or condition. Once a subject is enroled, all AEs must be reported through follow-up period. Only exacerbated conditions or new onset qualify as an AE. Principal Investigator will assess severity, relatedness, serious or unexpected.
Alternative Surgical Intervention	A post-index procedure surgery, other than PUL, to treat BPH.
Acute Urinary Retention	Painful inability to void and a residual volume < 1500 mL.
Invasive BPH surgery	• Transurethral resection of the prostate (TURP) • Transurethral Laser (PVP, HoLEP or Interstitial) • Open Prostatectomy
Index procedure	The first procedure to which subjects are enroled.
Precipitated AR	Acute urinary retention that develops in response to a trigger such as UTI, anaesthesia, surgery, medications with sympathomimetic or anticholinergic effects.
Serious Adverse Event (SAE)	Serious Adverse Event (SAE) is defined as untoward occurrence that: (a) results in death; (b) is life-threatening; (c) requires hospitalisation or prolongation of existing hospitalisation (d) results in persistent or significant disability or incapacity; (e) consists of a congenital anomaly or birth defect; or (f) is otherwise considered medically significant by the investigator. (in-patient hospitalisation is at least 24 consecutive hours)
Unexpected Adverse Event	An unexpected adverse event is an event which by nature, incidence, severity or outcome has not been identified in the current version of the Sponsor risk management files.
Spontaneous AR	Associated with older age, BPH, elevated PSA, or presence of severe LUTS.
PUL Procedure Time	Time from first device insertion to last device removed.

4 Introduction

Benign prostatic hyperplasia (BPH) impacts quality of life by causing lower urinary tract symptoms (LUTS). The number of U.S. men with symptomatic BPH that seek treatment options is projected to

increase from 8.1 million in 2010 to 10.3 million in 2020.[1] Current treatment options consist of watchful waiting, medical therapy and interventional procedures. Watchful waiting is generally reserved for those with mild symptoms.[2,3] Over 4 million U.S. men are on medical therapy for BPH.[4] While symptom relief is modest with an American Urological Association Symptom Index (IPSS) improvement at 1 year of 3.5-7.5 vs. 0-5.7 for placebo, the incidence of side effects along with inadequate relief prompt over one-quarter of men on drug therapy to discontinue treatment early.[2,4,5,6]

Most surgical approaches remove prostate tissue and, while highly effective, present with significant morbidity. The gold standard remains transurethral resection of the prostate (TURP) that is associated with a 14.9 point improvement in IPSS at 1 year.[2] This improvement, however, also comes with a 20% rate of perioperative morbidity and long-term complications that include urinary incontinence (3%), urethral stricture (7%), erectile dysfunction (10%) and ejaculatory dysfunction (65%).[2,7] Because tissue is removed and underlying tissue injured, there is a healing response and tissue inflammation such that subjects experience routine catheterisation and irritative symptoms post-procedure.[2] For these reasons, the number of TURP surgeries among the US Medicare population has been declining (from 72,163 in 1999 to 49,683 in 2005).[8] Laser vaporisation is a newer approach to TURP that minimises blood loss compared to conventional TURP, but still typically requires general or spinal anaesthesia and overnight hospital stay. There is routine catheterisation and post-operative dysuria, again as a result of tissue removal and injury.[7] US Medicare data show that from 2005 to 2007, conventional TURP surgeries decreased by over 12,600 procedures while laser vaporisation procedures increased by over 12,100 procedures.[9] Thus, laser vaporisation has been employed more as a

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1 Roehrborn, C.G., Current medical therapies for men with lower urinary tract symptoms and benign prostatic hyperplasia: achievements and limitations, Rev Urol 2008; 10:14.

2 Benign Prostatic Hyperplasia Guideline, Roehrborn, C.G., McConnell, J.D., Barry, M.J., Benaim, E., Bruskewitz, R.C., Blute, M.L., Holtgrewe, H.L., Kaplan, S.A., Lange, J.L., Lowe, F.C., Roberts, R.G., Stein, B.S.: Guideline on the Management of Benign Prostatic Hyperplasia. American Urological Association Education and Research, Inc., 2003.

3 Kaplan, S.A., AUA guidelines and their impact on the management of BPH: an update, Rev Urol 2004; 6 (Suppl 9): S46.

4 IMS Health Pharmaceutical Data.

5 Emberton, M., Fitzpatrick, J.M., Garcia-Losa, M., Qizilbash, N., Djavan, B., Progression of benign prostatic hyperplasia: systematic review of placebo arms of clinical trials, BJU International 2008; 102 (8): 981-6.

6 Verhamme, K.M.C., Dieleman, J.P., Bleumink, G.S., Bosch, J.L.H.R., Stricker, B.H. Ch., Sturkenboom, M.C. J.M., Treatment strategies, patterns of drug use and treatment discontinuation in men with LUTS suggestive of benign prostatic hyperplasia: The Triumph Project, European Urology 2003; 44: 539.

7 Miano, R, De Nunzio, C., Asimakopoulos, A.D., Germani, S., Tubaro, A., Treatment options for benign prostatic hyperplasia in older men, Med Sci Monit 2008; 14: RA94.

8 Yu, X, Elliott, S.P., Wilt, T.J., McBean, A. M., Practice patterns in benign prostatic hyperplasia surgical therapy: the dramatic increase in minimally invasive technologies, J Urol 2008; 180: 241.

9 Medicare data calculated from the Medicare Physician/Supplier Procedure Summary Master File, 2004-2007.

replacement for conventional TURP while the total number of TURP surgeries (inclusive of laser vaporisation) has been stable or is decreasing slightly.

Thermotherapies such as transurethral microwave therapy (TUMT), transurethral steam injection (TSI) and transurethral needle ablation (TUNA) induce necrotic scarring of the prostate as a replacement for surgical resection.[8] The effectiveness is greater than that of drugs but less than that of TURP (10.2 and 9.1 point improvement in IPSS at 1 year for TUMT and TUNA, respectively).[2] There is a significant shortcoming of these thermotherapies that the subject experiences within the initial months after treatment. By nature of inducing thermal injury to the prostate, there is a healing response, tissue inflammation and irritative voiding symptoms in virtually all subjects.[2] Post-procedure, subjects face routine catheterisation, a 20-25% risk of acute urinary retention, and irritative voiding symptoms that last for 4-6 weeks.[2,7] During the Prostalund Coretherm IDE study, the three TUMT patient groups experienced 14, 18, and 20 days mean post-treatment indwelling catheter time.[10] In addition, TUMT therapies have been associated with > 20% retrograde ejaculation rate.[11,12] Thus, procedure volumes for thermotherapies among Medicare beneficiaries only increased gradually to modest levels of 37,637 in 2005 and have been declining since.[8,9]

With a high prevalence of subjects who discontinue medical therapy and a relatively low incidence of interventional treatment, there is a large subject population that remained inadequately addressed until the advent of the Prostatic Urethral Lift (PUL) procedure. The UroLift® System was originally approved via De Novo (DEN130023) and Special 510(k) K133281. PUL is a tissue-sparing minimally invasive treatment for BPH, is based on the hypothesis that LUTS secondary to BPH could be treated by mechanically disassociating the obstructing prostatic lobes instead of removing or injuring prostate tissue, thereby offering the ability to relieve symptoms with low morbidity and a better subject experience. At one year, subjects demonstrate an IPSS improvement similar to or better than thermotherapy (10.8 points), but the difference was the very low morbidity endured to reach that result.[13] Catheterisation was only 32% for a mean duration less than a day. IPSS significantly improved

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10 Summary of Safety and Effectiveness, Prostalund CoreTherm Microwave Therapy System, PreMarket Approval (PMA) Number P010055.

11 Norby, B, Nielsen, H.V., Frimodt-moller, P.C., Transurethral interstitial laser coagulation of the prostate and transurethral microwave thermotherapy vs transurethral resection or incision of the prostate: results of a randomized, controlled study in patients with symptomatic benign prostatic hyperplasia, BJU International 2002; 90: 853-62.

12 Ahmed, M., Bell, T., Lawrence, W.T., Ward, J.P., Watson, G.M., Transurethral microwave thermotherapy (Prostatron@version 2.5) compared with transurethral resection of the prostate for the treatment of benign prostatic hyperplasia: a randomized, controlled, parallel study, British Journal of Urology 1997; 79: 181-5.

13 Roehrborn CG, Gange SN, Shore ND, Giddens JL, Bolton DM, Cowan BE, Brown BT, McVary KT, Te AE, Gholami SS, Rashid P, Moseley WG, Chin PT, Dowling WT, Freedman SJ, Incze PF, Coffield KS, Borges FD, Rukstalis DB. Multi-Centre randomized controlled blinded study of the prostatic urethral lift for the treatment of LUTS associated with prostate enlargement due to BPH: the L.I.F.T. study. J Urol 2013; 190: 2162-2167.

by 2 weeks. There was, for the first time in a BPH device trial, no de novo sustained ejaculatory or erectile dysfunction.

5 Previous UroLift ® System Clinical Studies

5.1 Pivotal Randomised Study ("L.I.F.T.")

The L.I.F.T. study design was prospective, multicentre, multinational, 2:1 randomised, single-blinded controlled clinical trial of the UroLift System. The study had two phases, a randomised single-blind period followed by a non-randomised open-label period. The blinded randomised trial portion of the study started at the time of the procedure and ended at the subject's 3-month visit. The effectiveness assessment was double blinded in terms of both the subject and the assessor.

A total of 206 subjects were randomised in a 2:1 ratio, (UroLift: 140; Control: 66) at 19 investigational sites. Fourteen U.S. sites and 5 non-U.S. sites (three in Australia and two in Canada) participated in the investigation. Subjects in the UroLift group underwent the UroLift System procedure. Subjects in the Control group underwent a sham procedure, which included standard cystoscopy with perioperative sounds and verbal comments that mimicked the UroLift arm procedure. All subjects were blinded to the randomised treatment, and maintenance of the blind was assessed four times from procedure discharge up to and including the 3-month visit.

Once the 3-month follow-up was completed, the subjects were unblinded. After unblinding, if their symptoms returned and treatment was required, subjects were allowed to receive treatment/retreatment (either de novo treatment if originally in the Control group or as a retreatment if originally treated by PUL) with the UroLift System or any other approved BPH treatment.

5.1.1 Effectiveness Endpoints

At 3 months, the effectiveness of the UroLift System was demonstrated by comparison of the change from baseline of the International Prostate Symptom Score (IPSS) of the treated group to the Control group. At 3 months, in the ITT population, treatment with the UroLift System resulted in a mean decrease of 11.1 (50.0%) in IPSS (IPSS 11.2±7.65 at 3 months vs. 22.2±5.48 at baseline). Subjects in the Control group demonstrated a decrease of 5.9 (24.2%) in IPSS (IPSS 18.5±8.59 at 3 months vs. 24.4±5.75 at baseline). Thus, the mean improvement in the UroLift group was 188% of the mean improvement in the Control group. Similar reductions in IPSS were observed in the PP population. In both populations, the null hypothesis was rejected with a p-value of less than 0.025 (ITT p value = 0.003; PP p value =0.014), demonstrating a statistically significant improvement in IPSS in the treatment group over the Control group. The effectiveness results demonstrated a clinically

meaningful improvement in IPSS as compared to Control under blinded conditions in the first three months of the study.

At 12 months, the long-term effectiveness for subjects in the UroLift group was demonstrated by comparison of the IPSS at 12 months and at baseline. In the ITT population, treatment with the UroLift System resulted in a 45.5% reduction in IPSS (IPSS 11.7±7.32 at 12 months vs. 22.0±5.49 at baseline). Subjects in the PP population demonstrated a 47.6% reduction in IPSS (IPSS 11.3±7.04 at 12 months vs. 21.8±5.37 at baseline). In both the ITT and PP populations the null hypothesis was rejected, with the lower bound of the 97.5% confidence interval demonstrated to be greater than 30% (ITT lower bound 38.3%; PP lower bound 42.8%).

Subjects were followed through five years. LUTS severity (IPSS), quality of life, Qmax, sexual function, and adverse events were assessed throughout follow up.

Procedural Results

One hundred and forty (140) procedures were performed as part of the initial UroLift randomisation. The procedure was considered successful if the post treatment cystoscopy (as determined by an independent reviewer of all available day-of-procedure cystoscopies) exhibits an increase in the urethral opening post-treatment and the subject is free of device/procedure-related serious adverse events (SAEs) immediately (defined as within the same calendar day) post treatment. Procedural success for UroLift ITT subjects was 99.2% for the 120 subjects for which cystoscopy video was available, as shown in Table 3. Although cystoscopy videos were either not obtained or were not readable to confirm procedural success for the remaining 20 UroLift System subjects, it is important to note that no other day-of-procedure SAEs were reported in this group.

Table 3 L.I.F.T. Procedural Success

Procedural Success Definition	Procedural Success, % (n/N)	95% C.I.
An increase in urethral opening on cystoscopy post-treatment -AND- Subject is free of device/procedure-related SAEs immediately (i.e., the same day) post treatment	99.2 (119/120)[1]	(95.4, 99.98)

[1] One subject had a device-related and procedure-related SAE of Haematuria on the day of procedure.

Procedure information for the randomised subjects in both study groups, including prophylactic antibiotics, anaesthetic/sedation, procedure time, and catheter placed at discharge time, is summarised in **Table 4**. The majority of subjects in the study received topical anaesthesia for their procedure, which was used in equal proportions in the UroLift System (90.7%) and Control (90.9%) groups. Subjects may have had more than one type of anaesthesia and/or sedation. It is an intended

design feature of the system to be able to perform the procedure with only local anaesthesia. One hundred thirteen (113) subjects in the UroLift group (80.7%) and 53 subjects in the Control group (80.3%) had the procedure done with topical anaesthesia only. Less than 20% of the UroLift and Control subjects had general anaesthesia. When general anaesthesia was given, it was primarily because it was the sites' standard procedure, not because it was determined to be medically indicated.

The majority of subjects in the UroLift group, 60.7% (85/140), were not catheterised. Catheters were placed in the UroLift System subjects at a higher rate than Control subjects, 39.3% (55/140) versus 10.6% (7/66), respectively, as would be expected in a sham-controlled study. Some investigators chose to use catheters prophylactically or as part of routine or standard of care in subjects in the UroLift group (**Table 4**).

Median procedure time, measured from subject preparation to time subject left procedure room, was somewhat longer in the UroLift group versus Control group, 63.0 versus 45.0 minutes, respectively, as would be expected.

Mean time to return to pre-operative activity level was longer in the UroLift System group than in the Control group (8.6 ± 7.53 days vs. 3.1 ± 4.38 days). This too would be expected given the greater degree of tissue manipulation required for device delivery in the UroLift group.

Table 4 L.I.F.T. Procedure Information

Procedure Component		UroLift (N = 140)	Control (N = 66)
		% (n/n responses)	
Anaesthesia	Topical / Lidocaine jelly	90.7 (127/140)	90.9 (60/66)
	Prostate block	1.4 (2/140)	3.0 (2/66)
	Spinal	0 (0/140)	0 (0/66)
	General	17.9 (25/140)	16.7 (11/66)
Prophylactic Antibiotics Used		100 (140/140)	100 (66/66)
Sedation	Oral	67.9 (95/140)	68.2 (45/66)
	Intramuscular	0.7 (1/140)	0 (0/66)
	Intravenous	30.0 (42/140)	33.3 (22/66)
Catheter Placed Prior to Discharge		39.3 (55/140)	10.6 (7/66)
		Mean, Median, SD [min - max], (n)	
Cystoscopic Intervention Time[1] (min)		24.4, 21.0, 12.45 [5 - 65], (140)	9.6, 8.0, 5.54 [2 - 25], (65)4
UroLift Procedure Time[2] (min)		18.7, 15.0, 11.07 [3 - 57], (140)	
Overall Procedure Time[3] (min)		66.2, 63.0, 23.84 [24 - 162], (140)	46.8, 45.0, 17.21 [18 - 100], (65)[4]
Time to Return to Pre-operative Activity Level (days)		8.6, 7.0, 7.53 [0 - 43], (140)	3.1, 2.0, 4.38 [0 - 28], (66)

Procedure Component	UroLift (N = 140)	Control (N = 66)
	% (n/n responses)	

[1]Defined as cystoscopic start time to procedure end time.
[2]Defined as time from 1st device insertion to last device removal.
[3]Defined as start of anaesthesia time to time subject leave procedure room.
[4]Subject 218-001 did not have a procedure end time recorded, thus only 65 cystoscopic intervention times and overall procedure times are available.
Source: de novo one year report

5.1.2 Safety Assessment

There were no unanticipated adverse effects observed for any subject in the study through the 5-year follow-up, nor any de novo sustained ejaculatory or erectile dysfunction events. During the blinded phase of the study, the Control group did not experience any serious adverse events (SAEs) related to the procedure. During the first three years post index in the primary UroLift group, 8 SAEs in 8 separate subjects were reported then adjudicated by Clinical Events Committee (CEC) as at least possibly related to either the device and/or procedure. One of the events occurred in the immediate post-operative period, one before the 12-month visit, and the remaining 6 occurred in long-term follow-up.

The primary safety endpoint was an assessment of the rate of extended post-operative urinary catheterisation in the subjects randomised to the UroLift group of the study in the ITT group. The extended post-operative urinary catheterisation rate was defined as only including those subjects who required catheterisation within the first 3 days as part of post-operative management for inability to void, and required the catheter for more than 7 days.

To meet the primary safety endpoint, the upper bound of a one-sided 97.5% exact binomial confidence interval of the observed rate of extended post-operative urinary catheterisation >7 days was required to be less than or equal to 10%. Subjects who had a catheter inserted within 3 days but required additional non-pharmacological intervention prior to the end of the 7-day insertion period were counted as having an event for this endpoint.

The study met the primary safety endpoint, with only 1.4% (2/140) of the UroLift System subjects having an extended post-operative urinary catheterisation greater than 7 days. The upper bound of the 97.5% CI for this rate was 5.1%, thus meeting the primary safety endpoint. While each of these subjects underwent extended post-operative catheterisation, it is noted that the effectiveness of the procedure was not negatively affected. The first subject experienced a 55% IPSS reduction by 1 month that increased to a 64% reduction by 12 months, and the second subject experienced 1- and 12-month IPSS reductions of 65% and 71%, respectively.

5.2 BPH-6: A UroLift System Post Market Multi-Centre Randomised Study

Lower urinary tract symptoms secondary to benign prostatic hyperplasia affect the quality of life of many men. A significant number of these men value preserving sexual function, continence and safety as much as mitigating their LUTS. For these men an effective therapy might best be defined by meeting a composite endpoint, termed "BPH-6 endpoint". The BPH-6 therapy effectiveness is defined as the ability to achieve all of the subject's most important goals: 1) adequate relief from LUTS, 2) rapid return to normal activity, 3) maintenance of erectile function, 4) maintenance of ejaculatory function, 5) maintenance of continence, and 6) avoidance of high grade perioperative complications. Comparing the UroLift System treatment to the standard of care, TURP, by means of the BPH-6 composite endpoint will assist urologists and healthcare systems in determining the proper position for the UroLift System treatment as a treatment for LUTS secondary to BPH.

This study provided the first randomised comparison of PUL and TURP in men suffering from LUTS secondary to BPH. Both study procedures effectively mitigated LUTS. Analysis of the composite BPH-6 endpoint demonstrated that TURP was superior in reducing IPSS ($p = 0.05$), whereas PUL was superior for preservation of ejaculatory function and quality of recovery ($p < 0.0001$). One objective of a less invasive procedure is to improve surgical recovery. The recovery period after TURP can last from weeks to months, and may be disruptive for subjects and their families[14]. This is likely the first study to quantify recovery experience after TURP on a visual analog scale, and it gives a powerful indication of subject experiences. The number of participants who experienced the BPH-6 definition of high-quality recovery (VAS $\geq$ 80% by one month) was greater for PUL than for TURP (64% vs 44%).

No significant differences were observed for erectile dysfunction, incontinence, or grade II+ adverse events.

5.3 UroLift System

The UroLift System is manufactured by NeoTract, Inc. and consists of a delivery system (**Figure 1**) and a UroLift Implant (**Figure 2**) comprised of a nitinol Capsular Tab (CT) that rests on the outer capsule of the prostate and a stainless steel Urethral End-Piece (UE) that rests on the urethral wall. The CT and UE are connected by a length of Polyethylene Terephthalate (PET) monofilament suture. During the Prostatic Urethral Lift procedure, customised transprostatic implants are placed to hold open the obstructing prostatic lobes and expand the urethral lumen (**Figure 3**). The UroLift System is inserted

[14] Mogensen K, Jacobsen JD. The load on family and primary healthcare in the first six weeks after transurethral resection of the prostate. Scand J Urol Nephrol. 2008;42(2): pp. 132-136.

transurethrally through a rigid sheath under cystoscopic visualisation. When the targeted area of the encroaching lateral prostatic lobe is located, the lobe is displaced by applying an outward pressure away from the urethra such that the obstructive lobe is compressed and the prostatic fossa enlarged. By applying this force, the effect of lifting the lobe can be tested before delivering an implant. A 19 gauge needle is then deployed from the tip of the delivery device extending from the intraluminal urethral wall through the prostatic capsular surface. The CT is then delivered through the hollow bore of the needle. As the needle is retracted, the CT engages the capsular prostatic surface and settles into a stable position, tension is applied, and the UE is secured onto the monofilament apposed to the urethral wall. Because the fibromuscular capsule is less compliant than the peri-urethral tissue, the CT holds firmly in place while the UE holds the lobe in its displaced position thus expanding the urethral lumen. When implanted, the UE can invaginate into the urethral wall, which reduces the foreign material surface area exposed to the urine stream and can lead to complete epithelialisation over time. Migration can be prevented by the nature of anchoring the implant in place.

Based on the US FDA IDE L.I.F.T. Study, the UroLift System has exhibited a clinically meaningful improvement in lower urinary tract symptoms (LUTS) as early as 2 weeks post procedure that can be sustained through at least one year with an adverse event rate (e.g., catheterisation post treatment) that is equal to or lower when compared to other minimally invasive surgical therapies. This study led to FDA clearance by demonstrating the safety and effectiveness of the UroLift System for the treatment of BPH.

Figure 1 UroLift Delivery Device

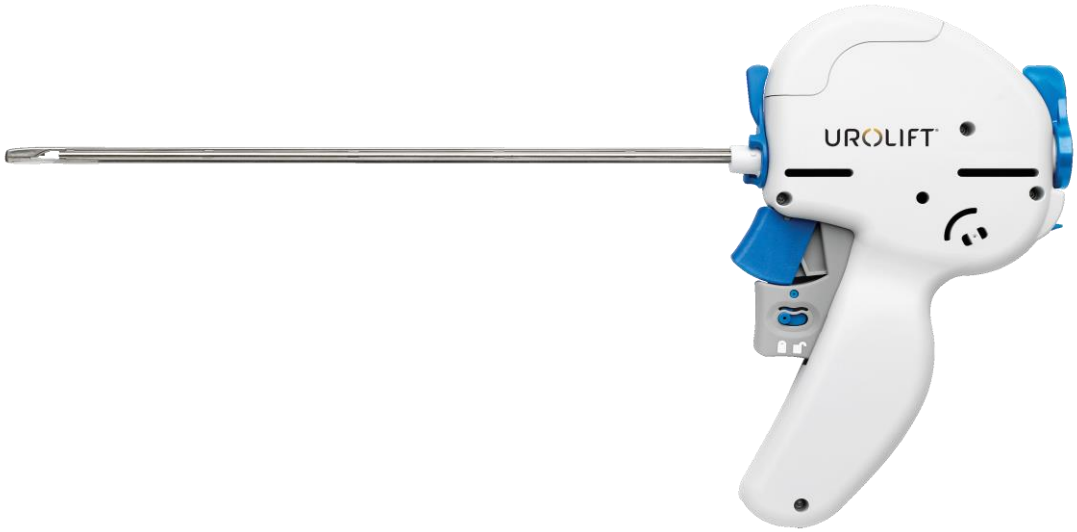


Figure 2 Components of UroLift Implant

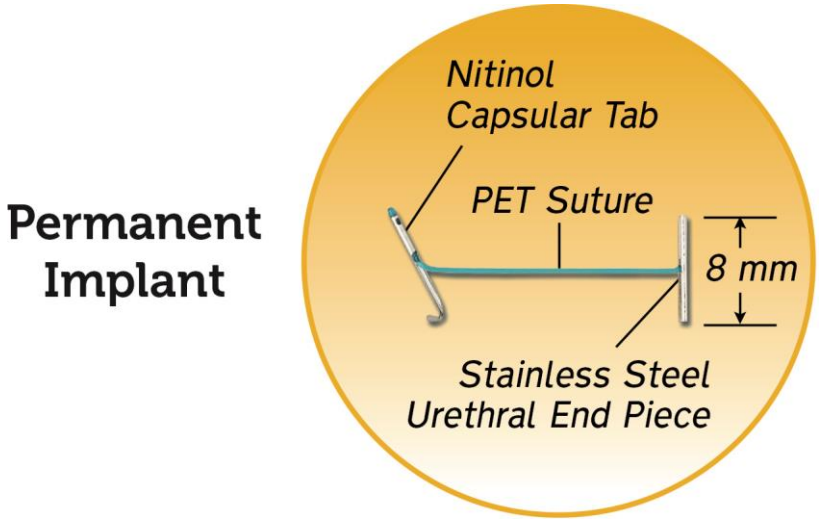
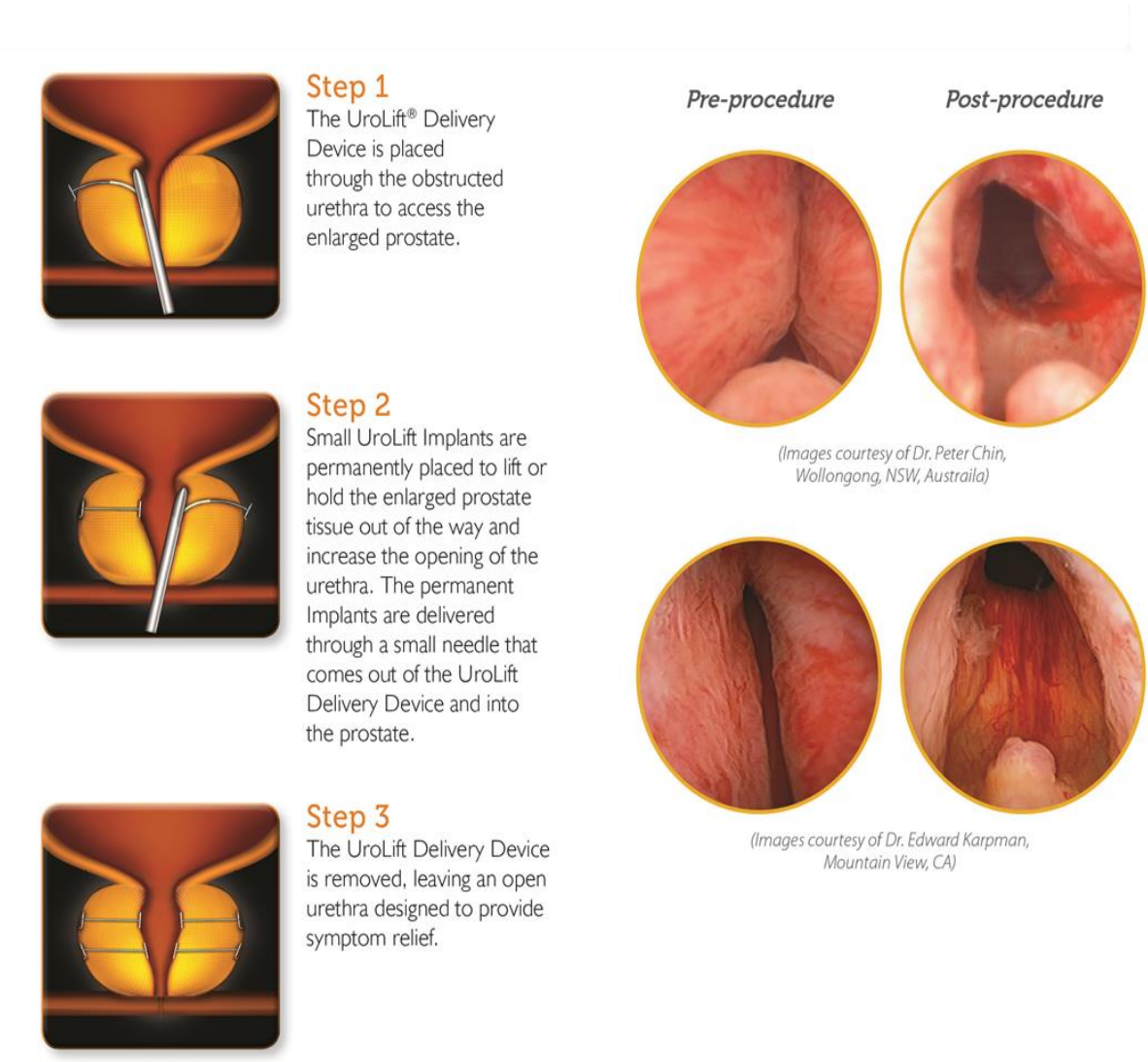


Figure 3 Steps of UroLift procedure; Obstruction of the prostatic urethra before and after images



5.3.1 Indication for Use

The UroLift System is indicated for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men 50 years of age or older.

5.3.2 Instructions for Use

A copy of the Instructions for Use (IFU) accompanies each device when shipped.

6 Rationale

Acute urinary retention (AR) represents end-stage, painful, absolute failure to void urine and is associated with a significant morbidity. The majority of cases in men (53[15]-65%[16]) usually result from the progressive obstruction to the bladder outlet due to benign prostatic enlargement[17] (BPE). The published incidence of AR due to BPH varies widely from 0.4% to 25%[18]. The variability is partially due to the heterogeneous definition of acute retention, spontaneous AR, and level of evidence available. Alternatively, precipitous triggers for AR may include: prostate cancer, prostatitis, lower urinary tract infection (UTI), constipation, urethral stricture, genitourinary trauma, neurological injury or compromise. Potential contributory factors may include age, prescription drugs (e.g. anticholinergics, centrally acting drugs, alpha agonists), alcohol, and anaesthetics. It is unusual for AR to affect men under the age of 50 years where risk was found to be 1.6%, whereas men aged 70-79 years are at 10% risk of AR[19].

The current treatment pathway for men suffering their first episode of AR is delineated in **Figure 4**. The immediate steps are evidence based supported consistently with catheterisation paired with alpha blocker use doubling the rate of spontaneous voiding without catheter against placebo, typically 60% success (60% vs. 37% placebo)[20]. In the 40% that fail the trial without catheter (TWOC), Fitzpatrick[21] reports among a 6000+ survey of AR management that 49% were recatheterised and had BPH surgery, while the majority (44%) of the others repeated a subsequent TWOC with a success rate of 29.5%. The majority of patients with BPE that have an episode of AR will eventually elect a surgical resolution.

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[15] Choong, S. and Emberton, M. (2000), Acute urinary retention. BJU International, 85: 186–201. doi:10.1046/j.1464-410x.2000.00409.x

[16] Elhilali M, Vallacien G, Emberton M, et al. Management of acute urinary retention (AUR) in patients with BPH: A worldwide comparison. J Urol. 2004; 171:407.

[17] Roehrborn CG, Bruskewitz et al: Urinary retention in patients with BPH treated with finasteride or placebo over 4 years. Characterisation of patients and ultimate outcomes. The PLESS Study Group. Eur Urol 2000; 37: 528.

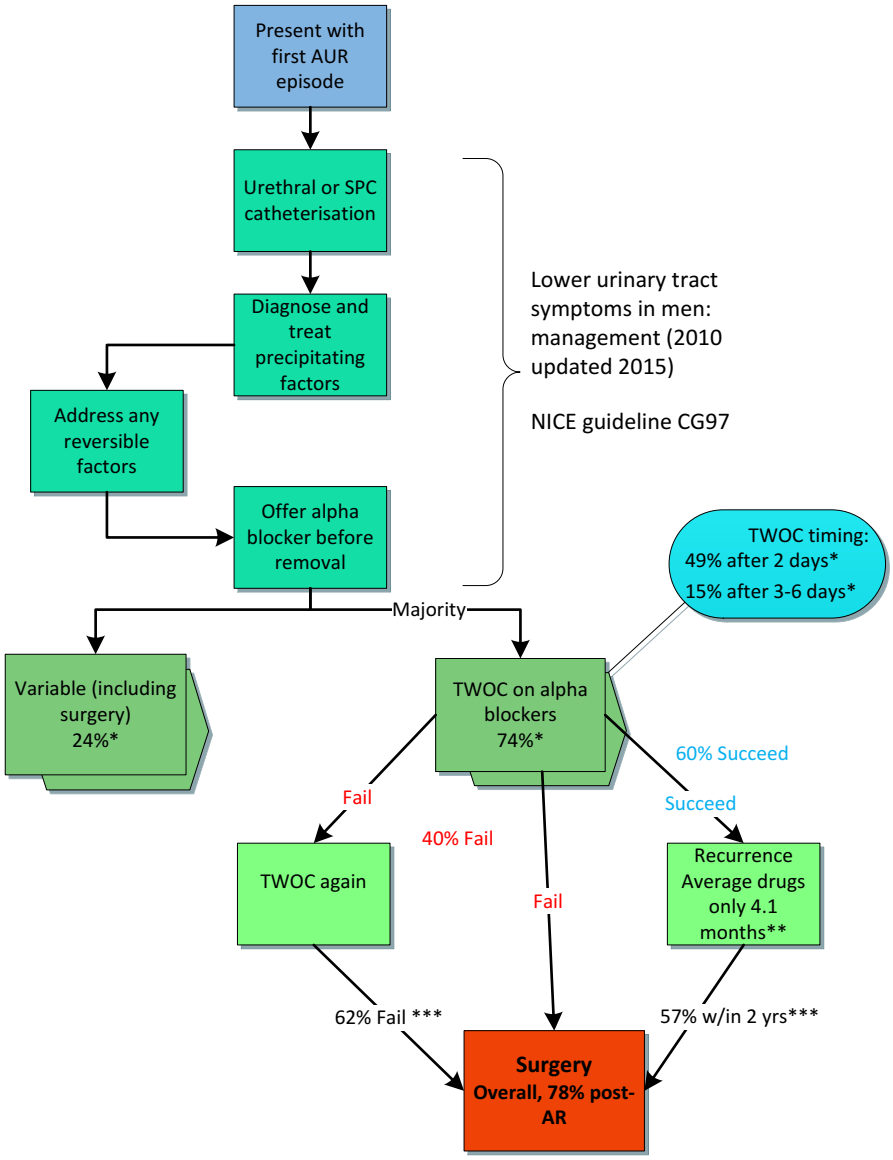
[18] Hartung, R; Do Alpha-blockers prevent the occurrence of Acute Urinary Retention? Eur Urol. 2001; 39 (13-18).

[19] Jacobsen SJ, Jacobson DJ, German CJ et al. Natural history of prostatism: Risk factors for acute urinary retention. J Urol. 1997; 158:481-7.

[20] McNeill SA, Daruwala PD, Mitchell ID, Shearer MG,Hargreave TB. Sustained-release alfuzosin and trial without catheter after acute urinary retention: a prospective, placebo-controlled. *BJU International* 1999;84 (6):622–7.

[21] Fitzpatrick, John M et al. "Management of Acute Urinary Retention: A Worldwide Survey of 6074 Men with Benign Prostatic Hyperplasia." *Bju International* 109.1 (2012): 88–95. *PMC*.

Figure 4 Current Treatment Pathway for Acute Urinary Retention [22,23,24,25]



See citations for *

[22] Manikandan, R., Srirangam, SJ et al. Management of acute urinary retention secondary to benign prostatic hyperplasia in the UK: a national survey. BJUI. 2004, V 93 (1) 84-88.

[23] Fitzpatrick, John M et al. "Management of Acute Urinary Retention: A Worldwide Survey of 6074 Men with Benign Prostatic Hyperplasia." *Bju International* 109.1 (2012): 88–95. *PMC*.

[24] Roehrborn CG, Bruskewitz et al: Urinary retention in patients with BPH treated with finasteride or placebo over 4 years. Characterisationof patients and ultimate outcomes. The PLESS Study Group. Eur Urol 2000; **37:** 528.

[25] McNeill S.A, The Role of Alpha-Blockers in the Management of Acute urinary Retention Caused by Benign Prostatic Obstruction. E Urol. 2004, 45, 325-332.

Men failing a single TWOC have limited options to restore voiding. Long-term catheter management may be elected, either indwelling or intermittent clean catheterisation (CISC), which carries a burden of maintenance and frequent UTIs (over half will experience). Catheter use carries with it risk of haematuria, and less common AEs such as urethral diverticula and ischemic necrosis of the penis[26]. Many patients will opt instead to undergo an invasive BPH surgery such as TURP, PVP or HoLEP. These surgical options are known to be effective in treating BPH, however, the safety and recovery profile are more severe than a minimally invasive procedure including possible permanent sequelae. The complication rates vary depending on procedure, but common to all include infection, bleeding, pain, stress incontinence, sexual dysfunction, incontinence, delayed recovery up to 3-6 months and re-treatment. The other reality of invasive surgery in U.K. is the long waiting period to secure OR time that extends time on catheter significantly. The waiting period averages 30 weeks to procedure after counselling the patient.

The early UroLift studies described in section 5 above excluded subjects in urinary retention in order to provide non-confounding data on subjects with possible advanced bladder disease. The clinical studies also required BPH medication washout which is known to be effective in short term treatment of AR. This population is not contraindicated; however, no study yet exists to assess if its efficacy and safety are similar to the voiding subjects. The UroLift System is designed to immediately de-obstruct the prostatic lobes without tissue damage, thereby reducing the pressure required to initiate micturition. Because of this mechanism, it is hypothesised that urinary retention may resolve after PUL removes the mechanical cause of the AR. The PUL technology could offer patients a shorter wait time, and a safety profile that could be an attractive option for AR patients. As discussed above, the PUL procedure is a minimally invasive technique for BPH patients with demonstrated effectiveness and majority of adverse events mild or moderate and transient. Recovery to normal activity was reported at 8-9 days in the L.I.F.T. study. Additional benefits include short operative times, minimal bleeding, shorter hospital stay and maintenance of normal sexual function. Treatment under local anaesthesia is an emerging technique offering rapid treatment and recovery in the clinical setting.

6.1 Objectives

This study aims to assess if patients with acute urinary retention, who have failed at least one prior TWOC will benefit from the UroLift System. Additionally, this study will determine best practices, endpoint, and feasibility of performing a larger study. Finally, this study will compare the benefits and

[26] J Family Med Prim Care. 2016 Jul-Sep;5(3):539-542. doi: 10.4103/2249-4863.19726

risks of the PUL procedure with a retrospective matched population that underwent an invasive surgery such as TURP/HoLEP for AR.

6.2 Primary Study Assessment

The primary study assessment will be successful trial without catheter (TWOC). Success is defined as a spontaneous voided volume of ≥ 100 mL associated with a post void residual volume by ultrasound < 300 mL at 3 days (± 1 day) post index procedure.

6.3 Primary Safety Assessment

Rate of serious adverse events (SAEs) related to BPH intervention through 3 months.

6.4 Other Assessments

Several other outcomes will be analyzed during the 12 month follow-up to understand post-TWOC durability:

- Catheter free rate and days free from catheter at 1 month and throughout follow-up
- Number of subjects who failed initial attempt but are able to void in subsequent TWOC
- Need for further clean intermittent self-catheterisation (CISC)
- Urinary symptoms peak flow rate, post void residual (PVR) volume
- Subjects free from alternative surgical procedure for BPH
- Duration of pre-index procedure catheter and its impact on durability
- Rate of adverse events
- The prospective arm will be compared to the available data collected in the retrospective surgical arm

7 Study Design

The study is a multi-centre, consecutive, prospective feasibility study of the UroLift System in acute urinary retention (AR) patients. A retrospective dataset (patients treated from June 1, 2015 to December 31, 2015) of patients meeting similar criteria that underwent an invasive procedure to treat AR will be analysed against UroLift data. A maximum of 55 subjects undergoing UroLift will be enroled in up to six study centres in Great Britain. This feasibility study is the first to assess patients undergoing PUL with AR and will determine if a larger, quantitative study should be conducted with optimal methodology. By evaluating results pertaining to study design, primary study assessment, conduct of trial, site performance, subject compliance, and inclusion criteria specifically, a robust safety and effectiveness study can follow.

Clinical improvements will be assessed at post-procedure, 6 weeks, and months 3, 6, and 12 post-index procedure.

8 Enrolment Criteria

8.1 Inclusion Criteria

Subjects enroled in this clinical study must meet all of the following criteria.

1. Male gender
2. Diagnosis of symptomatic BPH
3. Age ≥ 50 years
4. Prostate volume ≤ 100 cc per ultrasound (US)
5. Acute urinary retention with at least one failed trial without catheter (TWOC) while on alpha blocker

8.2 Exclusion Criteria

Subjects will be excluded from the study if any of the following conditions apply.

1. An obstructive or protruding median lobe of the prostate
2. Previous BPH surgical procedure
3. Previous pelvic surgery (i.e. incontinence sling, trauma repair, penile implants, artificial sphincter) or irradiation
4. Urethral conditions that prevents insertion and delivery of device system into bladder (i.e. urethral strictures, meatal stenosis, bladder neck contracture)

5. Chronic retention volume of >1500 mL
6. Has not had prostate cancer excluded
7. History of prostate or bladder cancer
8. Biopsy of the prostate within the 6 weeks prior to Index Procedure
9. History of neurogenic or atonic bladder
10. Acute or chronic renal failure
11. Known coagulopathies or subject on anticoagulants within 3 days of index procedure (excluding up to 100mg ASA)
12. Known bladder stones within the prior 3 months or treatment within 12 months
13. Prostatitis requiring treatment (antibiotics) within the last year
14. Other co-morbidities that could impact the study results such as:
    - severe cardiac arrhythmias uncontrolled by medications or pacemaker
    - congestive heart failure NYHA III or IV
    - history of uncontrolled diabetes mellitus
    - significant respiratory disease in which hospitalisation may be required
    - known immunosuppression (i.e. AIDS, post-transplant, undergoing chemotherapy)
15. Life expectancy estimated to be less than 5 years
16. Desire to maintain fertility post procedure
17. Unable or unwilling to complete all required questionnaires and follow up assessments (e.g. lives out of area)
18. Unable or unwilling to sign informed consent form
19. Currently enroled in any other clinical research trial that has not completed the primary endpoint

Refer to Section 15.3 for the modified enrolment criteria for the retrospective arm.

9 Withdrawal Criteria

Subjects who have signed an informed consent form may be withdrawn from this study if they become unwilling or unable to comply with follow-up requirements, if they withdraw their consent, or if the investigator determines the subject should no longer continue in the study. Regardless of the

reason for withdrawal, data available for the subject at the time of withdrawal, including the reason for withdrawal, will be collected and entered in EDC. All practical efforts will be made to obtain the final AR status, retreatment status, and IPSS information.

10 Subject Procedures: Prospective Cohort

10.1 Subject Identification and Recruitment

Potential candidates for study will be identified through several paths (See **Figure 4**) with close oversite of the PI. The enrolment rate targeted is (2) subjects per month at each site which will be accomplished only if PI plays an active role in recruitment. PI contribution will vary per site, but could include training additional staff (such as research fellows), reviewing medical records with or in parallel to Research Coordinating Nurses (RC), and implementing awareness programs for local consultants and GPs. A plan should be established for a focused and efficient review of NHS medical records, along with monitoring BPH surgery waiting lists. Weekly time should be budgeted to execute the review plan and to discuss progress within the research team. Direct advertising is not planned, but may be implemented if enrolment proves challenging. The study will be posted on clinicaltrials.gov in advance of first subject, and other similar websites may be added. Sponsor may host web based meetings for the Research Coordinators to share expertise and troubleshoot any recruitment obstacles. Study accoutrements for recruitment will be provided by Sponsor such as posters, post-cards, and template letters to physicians, and language to post on research websites, provided they are first approved by the EC if intended for patients.

10.2 Screening Procedures

10.2.1 Informed Consent Process

The investigator or trained designee will discuss the study background along with the benefits and risks of the PUL procedure, participation, and other study procedures. Ample time and opportunity for candidate to inquire about details of the trial and to decide whether or not to participate in the trial should be given. All questions about the trial should be answered to the satisfaction of the subject, or the subject's legally acceptable representative.

For this study, the potential subject must sign the consent form that has been approved by the study site's Ethics Committee (EC). Failure to provide informed consent renders the subject ineligible for the study.

Subjects who appear to generally meet the study Inclusion/Exclusion criteria will be asked to sign the EC approved Informed Consent form before any study-specific tests or procedures are performed.

A copy of the signed and dated written consent form shall be given to the subject, an original shall be filed in the subject's medical record, and a copy maintained with the site's research documentation. Subjects should first sign the informed consent prior to undergoing any non-standard of care testing required by this study protocol.

Throughout the study, should there be important updates to the protocol and/or additional risks identified, a new EC approved consent form will require the subject's signature and date.

10.2.2 Determining Eligibility

To minimise stress and discomfort to the subject, some of the procedures that were documented and performed prior to subject informed consent, but within the timeframes specified below (

Table 5) may be used as a guideline for eligibility and baseline data. To further minimise burden on the subject, some eligibility tests are allowed on day of index procedure, therefore, proper expectations and alternatives will be discussed and planned with the subject. **Table 5** below provides a guideline of each of the inclusion and exclusion criteria timeframe and instructions. Subjects enroled without meeting all criteria will be considered a significant violation, and data may be excluded from analysis.

Table 5: Eligibility Procedures

Screening activity	Relevant Eligibility Criteria	Time Frame	Instructions
Ultrasound	• Prostate volume ≤ 100 cc per ultrasound rule out enlarged middle (median) lobe	During screening or just prior to procedure unless on file within 6 months of Index Procedure.	• Can be utilised if performed within 6 months of UroLift procedure/ enrolment, provided there is source documentation. • See section 10.13.2 for instructions.
Cystoscopy	• Urethral conditions that prevent insertion • Rule out obstructive or protruding median lobe	In screening or adjacent to (prior) on day of index procedure.	• Complete eCRF for cystoscopy performed. • Save digital recording and submit to NeoTract.
Medical History by PI assessment	• Life expectancy estimated to be less than 5 years • Co-morbidities that could impact the study • Diagnosis of symptomatic BPH • Acute or chronic renal failure • Chronic retention volume of >1500 mL	In screening up to index procedure; PI assessment should be as close to index procedure as possible.	• Patients with terminal conditions will be excluded. • Significant co-morbidities that impact life expectancy or ability to return for follow-up, or exposes patient to unreasonable risk should be excluded. • AR precipitated for reasons other than BPH must be confirmed and excluded. • Signs of renal failure should be ruled out per SOC.

Screening activity	Relevant Eligibility Criteria	Time Frame	Instructions
Medical History by medical database	• Prostatitis requiring treatment (antibiotics) within the last year • Known bladder stone within the prior 3 months or treatment within 12 months • Previous BPH or pelvic surgical procedure • Prostate or bladder cancer history • Prostate biopsy (allowed if negative and ≥6 wks) • Neurogenic or atonic bladder • If available, pre-procedure IPSS, peak flow rate, and PVR within 6 months	In screening up to index procedure; review of database should be completed as close to index procedure as possible.	• These criteria should be confirmed through patient interview and consistent with medical chart. Diagnostic testing not required unless symptomatic. • A thorough medical history should be documented to assist with adverse event reporting after enrolment, as each AE will require assessing if pre-existing or new.
Medical History by patient interview	• Unable or unwilling to complete all required questionnaires and follow up assessments • Desire to maintain fertility post procedure • Currently enroled in any other clinical research study that has not completed primary endpoint	Prior to procedure	• Erectile health will be a part of the questionnaires and participants should be willing to complete.

10.2.3 Other Baseline Procedures

Any subject questionnaire should be completed by the subject in a private setting after receiving instruction from research personnel. The Research Coordinator should review questionnaires for completeness prior to enrolment. If a question is left unanswered or is uninterpretable, the coordinator should return the questionnaire to the subject, requesting that subject complete the missed or equivocal question(s).

Table 6 summarises the pre-procedure activities not intended to screen for eligibility, but pertain to patient risk, confounding factors, and obtaining baseline health status.

Table 6 Pre-Procedure Activities*

*Includes data collection and procedures that don't determine eligibility		
Activity	**Considerations and instructions**	**Time Frame**
Sexual Function Questionnaire	• A baseline SHIM should be completed if patients are sexually active within the previous 6 months.	• Recall period of 6 months; complete in screening as applicable.
Urodynamics	• Determine the grade of bladder outlet obstruction (BOO) and to assess detrusor contractility function	• During screening, after consent, within 30 days of index procedure. • Urodynamics testing may be performed at each study site if a testing facility is available and a qualified operator is on-site.
Medications	• BPH, LUTS; Sexual Function; GU; should be captured.	• Collect through 10 years history of non-transient prescriptions with approximate duration and indication.
Alpha Blocker	• It is required that subject was on alpha blocker at a minimum, through previous failed TWOC.	• Alpha blockers should be prescribed per site's standard of care throughout the duration of the study. Initiation and cessation should be documented on the concomitant medication log.
Aspirin	• If patient on regular dose ≤ 100 mg no washout required. • If patient takes PRN, instruct patient to avoid.	• 3 days prior to index procedure
Anticoagulants	• Patient should be cleared to washout or, excluded.	• 3 days prior to procedure
Catheter use	• Record history, type, duration, indication, of catheter, reason out	• Most recent

10.3 Enrolment

A subject is considered enroled if he has signed the approved informed consent form to participate in the study, has met all inclusion and exclusion criteria, and the first UroLift delivery device has been inserted. Once subject is enroled, adverse events need to be documented and reported.

10.3.1 UroLift System Procedure Instructions

The UroLift System procedure may be performed in the office setting, ambulatory surgical centre, or hospital utilising appropriate level of anaesthesia and sedation per institutional standards. Antibiotic therapy will be initiated on or prior to procedure day with the type of antibiotic and duration identified per institutional standards (e.g. a five day course of oral ciprofloxacin). The use of these agents will be recorded on the case report forms.

A pre-procedure cystoscopic visualisation should also be performed if not previously captured and recorded. Cystoscopy should include visualisation of full prostatic urethra and bladder neck and to plan implant placement. The cystoscopy and procedure recorded file should be de-identified and provided to NeoTract.

10.3.2 UroLift System Equipment

Per the Instructions for Use (IFU), the following ancillary equipment will be used:

1. 2.9 mm 0° telescope (i.e. NeoTract REF UL-SCOPE, Storz REF 10324AA, or equivalent)
2. 20F sheath (NeoTract REF UL-SHEATH, Storz REF 27026C, or equivalent)
3. Visual obturator (NeoTract REF UL-VO, Storz REF 27028CN, or equivalent)

The following equipment ("Retrieval Kit") should be used if desired or necessary to retrieve or remove part of the UroLift Implant during the procedure.

1. 4 mm 30° telescope (UL-SCOPE4 or equivalent)
2. Telescope bridge (UL-WBRIDGE or equivalent)
3. Endoscopic rigid grasper or rigid scissors

Facility equipment should include:

1. Cystoscopy camera, light box/cable and monitor, with video recording capability
2. Standard fluid irrigation system including new, sterile fluid tubing

All of the ancillary equipment, including the telescope, sheath, visual obturator, bridge and graspers must be sterilised per the respective manufacturer's instructions before and after use. NeoTract will loan needed ancillary equipment as needed to study facilities throughout the enrolment period.

10.3.3 Training in Prostatic Urethral Lift Procedure

Selected Principal Investigators in the study will have performed a minimum of 30 UroLift procedures. Each will have undergone the NeoTract Professional Education Program.

10.3.4 Post Procedure Instructions

After creating an unobstructed anterior channel, continue with cystoscopy to verify implants are not present in the bladder, or extending into the bladder vesical. Interrogate the bladder neck for protruding implants. If a protruding or exposed implant is present, it should be removed.

A urinary catheter will be placed prophylactically after the Investigator completes the UroLift procedure, and subject provided instructions on its proper maintenance. The subject should remain on

alpha blockers per the site's standard of care. Initiation and cessation should be documented on the concomitant medication log. A post-procedure follow-up visit to perform Trial without Catheter will be scheduled for 3 days (± 1 day) after index procedure.

The Investigator or designee will record the following procedural data:

- Device: number of UroLift devices used, location of implantation, lot number, performance
- Cystoscopy findings, including confirmation of inclusion criteria, stones, and other notable pathology
- Time: subject enters and leaves procedure room, first/last UroLift device, catheter placement
- Anaesthesia/sedation: duration, type, and delivery of procedural medications
- Clinical staff required during the procedure
- Complications/adverse events
- Venue type (clinic, outpatient, inpatient, etc.)
- Time to discharge or release from treatment facility
- Urinary catheter placement, type and timing (length)
- Medications used
- Post-operative interventions (if any)

10.4 Post-Procedure Trial Without Catheter (TWOC)

The subject will return to clinic **3 days (± 1 day)** after Index procedure for the primary study assessment screening of bladder function without catheter. TWOC will be considered successful if the spontaneous void is ≥100 mL with PVR < 300 mL. If subject fails the initial TWOC, at least one additional TWOC will be performed per standard of care. All catheterisations will be recorded on the eCRF.

The following evaluations will be performed in office **3 days (± 1 day)** after index procedure in conjunction with the TWOC:

- Relevant Concomitant medications: BPH/LUTS; Sexual Function; GU; Prostate Cancer
- Freestanding uroflow and post void residual (PVR)
- Catheterisation review
- Adverse Event review; Intervention review

10.5 6 Week Follow-up Procedures

The following evaluations will be performed in office **6 Weeks (± 7 days)** after index procedure:

- Questionnaires to be completed by the subject:

  - Urinary Symptoms questionnaires including IPSS & QoL (International Prostate Symptoms Score with Quality of Life) and BPHII (Benign Prostatic Hyperplasia Impact Index) unless current indwelling catheter.
  - SHIM (Sexual Health Inventory for Men): Recall period for this visit should cover only post-enrolment activity. Completed if subject was sexually active at baseline.
  - Return to Normal
  - Patient Satisfaction
  - Symptom questionnaire upon occurrence (includes: Incontinence Severity Index (ISI), haematuria, dysuria, pelvic pain VAS)
- Relevant Concomitant medications: BPH/LUTS; Sexual Function; GU; Prostate Cancer
- Urinalysis (urine culture and sensitivity if abnormal, clinically significant and indicates a urinary infection). UA not required if current indwelling catheter.
- Freestanding uroflow and post void residual (PVR)
- Voiding Assessment
- Catheterisation Review
- Adverse Event Review; Intervention Review

10.6 3 Month Follow-up Procedures

The following evaluations will be performed in office at **3 months (± 14 days)** post procedure:

- Questionnaires to be completed by the subject:
  - Urinary Symptoms questionnaires including IPSS & QoL (International Prostate Symptoms Score with Quality of Life) and BPHII (Benign Prostatic Hyperplasia Impact Index) unless current indwelling catheter.
  - SHIM (Sexual Health Inventory for Men): Recall period since the last visit or 6 week follow-up. Completed if subject was sexually active at baseline.
  - Return to normal if not already achieved
  - Patient Satisfaction
  - Symptom questionnaire upon occurrence (includes: Incontinence Severity Index (ISI), haematuria, dysuria, pelvic pain VAS)
- Relevant Concomitant medications: BPH/LUTS; Sexual Function; GU; Prostate Cancer
- Urinalysis (urine culture and sensitivity if abnormal, clinically significant and indicates a urinary infection). UA not required if current indwelling catheter.
- Freestanding uroflow and post void residual (PVR)
- Digital Rectal Exam (DRE)
- Voiding Assessment
- Catheterisation review

- Adverse Event review; Intervention Review

10.7 6 Month Follow-up Procedures

The following evaluations will be performed by telephone, unless Investigator elects to perform in office, at **6 months (± 14 days)** post index procedure:

- Telephone administration of subject questionnaires:
  - Urinary Symptoms questionnaires including IPSS & QoL (International Prostate Symptoms Score with Quality of Life) and BPHII (Benign Prostatic Hyperplasia Impact Index) unless current indwelling catheter.
  - Patient Satisfaction
  - Symptom questionnaires upon occurrence (includes: Incontinence Severity Index (ISI), haematuria, dysuria, pelvic pain VAS)
- Relevant Concomitant medications: BPH/LUTS; Sexual Function; GU; Prostate Cancer
- Voiding Assessment
- Catheterisation review
- Adverse Event review; Intervention review

10.8 12 Month Follow-up Procedures

The following evaluations will be performed at **12 months (± 30 days)** post index procedure:

- If subject is scheduled for or has already undergone alternative surgical procedure, see also section **10.10.1**.
- Questionnaires to be completed by the subject:
  - Urinary Symptoms questionnaires including IPSS & QoL (International Prostate Symptoms Score with Quality of Life) and BPHII (Benign Prostatic Hyperplasia Impact Index) unless current indwelling catheter.
  - SHIM (Sexual Health Inventory for Men): Recall over the last 6 months. Completed if subject was sexually active at baseline.
  - Patient Satisfaction
  - Symptom questionnaires upon occurrence (includes: Incontinence Severity Index (ISI), haematuria, dysuria, pelvic pain VAS).
- Relevant Concomitant medications: BPH/LUTS; Sexual Function; GU; Prostate Cancer
- Freestanding uroflow and post void residual (PVR) unless current indwelling catheter or adverse event does not permit.
- Urinalysis (urine culture and sensitivity if abnormal, clinically significant and indicates a urinary infection). UA not required if current indwelling catheter.
- Digital Rectal Exam (DRE)
- Urodynamics testing, if applicable to site

- Cystoscopy (flexible)
- Voiding Assessment
- Catheterisation Review
- Adverse Event Review; Intervention Review

10.9 Interim Visits

Testing or procedures performed for adverse events associated with BPH or LUTS should be recorded and entered into eCRFs throughout the duration of subject follow-up even if outside protocol visit windows.

10.10 Surgical Intervention

The following information will be collected in association with secondary interventions:

- Adverse Event leading to the intervention (Unless urinary retention- **See Section 14.3**)
- Date of procedure
- Type(s) of procedure(s) performed
- Pre-procedure diagnosis for undergoing procedure
- Complications (as Adverse Events)
- Count of UroLift implant removal(s) and placements, if applicable
- Catherisation use

10.10.1 Alternative Surgical Intervention

A subject with recurring urinary retention requiring catheter or other LUTS may require alternative surgical intervention (HoLEP, TURP, PVP, etc). The subject will remain in study through 12 months with the following abbreviated requirements:

1) Upon the surgery scheduling, study visits will no longer be required with the exception of the 12 month visit.
    a. If subject is on catheter during the final visit (12 month) the urinalysis and urinary symptoms will not be required. Ongoing adverse events and catheterizations will be required. Refer to **Table 7,** Schedule of Procedures.
2) Between reintervention and 12 month visit, only urological serious adverse events (SAE) should be reported.

10.10.2 Secondary PUL

A subject undergoing a procedure for UroLift implant removal (misplaced) or additional implant(s) placement will remain on their original follow-up visit schedule.

10.11 Treatment Failure

The early TWOC primary assessment is the standard data point to demonstrate urinary retention relief, however, does not consider long term durability. An independent urologist will review the outcomes of each subject and adjudicate if considered a treatment failure. The following outcomes will be reviewed to determine if a treatment failure:

(1) The number of successful and/ or failed TWOCs.

(2) Duration of dependence on indwelling catheter.

(3) Prescribed surgical intervention.

10.12 Subject Follow-up Rate

Investigative centres and Sponsor will collaborate to implement robust methods to retain subjects through their 12 months study visit. Appropriate management of the prospective clinical trial, proper screening of study subjects, and training of participating investigators, monitors, and study coordinators will mitigate the amount of missing data.

10.13 Protocol deviations

Throughout the conduct of the study, data will be reviewed by Sponsor for the presence of deviations. Study personnel will report any deviation from the study protocol or regulation upon occurrence. The EDC will facilitate comprehensive deviation reporting through programmed edit checks which will trigger a protocol deviation eCRF. Sponsor monitors will also review data and conduct for any deviations during on-site visits per the monitoring plan. Reporting deviations in this study will be important not only for parsing the per protocol analysis, to assess quality of study conduct, but also to detect areas that should be modified for a larger study.

The Sponsor will evaluate PD trends in relation to prevention: methods of mitigation or value of requirement to the goal and study scientific integrity. Any individual site with high deviation rate will be investigated for root cause, and preventative measures will be implemented.

Any serious breaches of the Protocol, or the conditions and principles of GCP in connection to this trial, will be reported to the Ethics Committee. A serious breach is likely to effect to a significant degree – (a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial.

Table 7 Schedule of Procedures

Tests and Assessments	Screening	Index Procedure Through Release	Clinic Visit Post-procedure (3 days ± 1 day)	Clinic Visit 6 Weeks (± 7 days)	Clinic Visit 3 Months (± 14 days)	Phone Visit[1] 6 Month (± 14 days)	Clinic Visit 12 Months (± 30 days)	Study Exit
Informed Consent must be documented prior to any procedures outside standard of care				**Urinary Symptoms and UA are not required if subject is on current indwelling catheter.**				
Subject Questionnaires								
Urinary Symptoms				X	X	X	X	
SHIM	If sexually active within the last 6			If sexually active at baseline	If sexually active at baseline		If sexually active at baseline	
Incontinence Severity Index				If reported	If reported	If reported	If reported	
Dysuria				If reported	If reported	If reported	If reported	
Haematuria				If reported	If reported	If reported	If reported	
Pelvic Pain VAS				If reported	If reported	If reported	If reported	
Return to Normal				X	X (if not previously achieved)			
Patient Satisfaction				X	X	X	X	
Subject Interview								
Medical History	X							
Concomitant Medications[2]	X	X	X	X	X	X	X	
Voiding Assessment				X	X	X	X	
Intervention Review	X		X	X	X	X	X	
Testing								
Freestanding uroflow; PVR[3]			X	X	X		X	
Urinalysis (UA)[3]	X			X	X		X	
Urine Culture and Sensitivity	If indicated			If indicated	If indicated		If indicated	
Investigator Completed								
DRE	X				X		X	
Urodynamics[3,6]	X[4]						X	
US	X[4]							
Cystoscopy (flexible)[3]	X[4]						X	
Procedure		X						
Catheterisation Review	X	X	X	X	X	X	X	
Trial Without Catheter (TWOC)			X[5]					
Adverse Event Review		X	X	X	X	X	X	
Subject Discontinuation								X

[1] Office or phone visit acceptable. If subject returns to clinic due to an AE, any testing will be entered in EDC as interim (if outside visit window).
[2] Relevant medications and interventions only: BPH, LUTS; Sexual Function; GU; Prostate Cancer.
[3] Uroflow strip chart recordings, abnormal UA and urine culture results, urodynamics reports, and cystoscopy videos collected in the study will be retained as a part of the dataset and must be redacted.
[4] Can perform day of procedure prior to (index) UroLift procedure to reduce site and subject burden.
[5] TWOC should be repeated per standard of care if first attempt unsuccessful.
[6] Urodynamics testing may be performed at each study site if a testing facility is available and a qualified operator is on-site.

10.14 Performance of Study Procedures

10.14.1 Lab tests

A urinalysis will be collected and analysed from an accredited and certified laboratory. Redacted abnormal urinalysis results and urine culture results will be uploaded into the EDC system. Documents supporting laboratory credentials along with normal ranges should be kept in study files. Urinalysis (UA) should be collected within 30 days prior to index procedure. As subjects in screening will be on a catheter due to urinary retention, UA results cannot be used exclusively to determine eligibility. Urinary tract infections and gross haematuria should be based on the medical opinion of the investigator and may supersede lab results. UA may be performed by dipstick or microscopic analysis. Urine cultures should be performed if UA abnormal, clinically significant and indicates a urinary infection. Digital rectal exam (DRE) should also support the investigator decision to enrol and detect abnormalities in follow-up.

10.14.2 Transrectal or Transabdominal Ultrasound

Transrectal ultrasound (TRUS) or abdominal ultrasound shall be performed to assess eligibility for prostate volume (≤ 100cc) and rule out enlarged median lobe (or "middle lobe"). In general, an intravesical prostatic protrusion (IPP) should be viewed under cystoscopy to rule out enlarged median lobe. Additional measurements will be taken to characterise the prostate including length, transverse width, and anterior/posterior width. The ultrasound procedure can be performed in advance or on index procedure day. Results will be recorded on an eCRF. Exams that were performed prior to screening but within 6 months of the index procedure, may be used instead of repeating for the study, provided there is source documentation.

10.14.3 Cystoscopy

A flexible cystourethroscopy (cystoscopy) shall be performed to determine eligibility for urethral tortuosity or strictures (i.e. ability to insert a 20F sheath), prostate and bladder neck morphology, calculus urinary, and presence of an enlarged median lobe contributing to obstruction. A pre-procedure cystoscopic visualisation may be performed to qualify for the study provided the subject is aware of the potential for not meeting enrolment criteria. The cystoscopy should be performed while digitally recording, and should adequately visualise the bladder, the full prostatic urethra, and bladder neck. An additional cystoscopy after

implant placement shall be performed to rule out the presence of protruding or exposed implants.

10.14.4 Urodynamic testing

Urodynamics are now widely accepted as the reference standard to determine the grade of bladder outlet obstruction (BOO) and to assess detrusor contractility function. It is of particular interest to characterise the contribution and extent that each participate is in the AR disease state. Urodynamics testing may be performed at each study site if a testing facility is available and a qualified operator is on-site.

To ensure consistency across visits, the equipment used for study procedures will have documented calibration per manufacturer standards that is copied to study files. Detailed urodynamic procedure will be outlined in the manual of operations (MOP).

10.14.5 Freestanding Uroflowmetry

Subjects will be asked to refrain from voiding for two hours prior to uroflow testing. Uroflowmetry shall be obtained with the subject in a standing position prior to any instrumentation. A bladder scan is recommended to be performed prior to voiding to assure that the subject has a bladder volume of at least 250 mL. Site should ensure the subject has a full bladder to increase the validatity of the uroflow. Results will be recorded for each void in the eCRF and redacted waveform strip recordings uploaded in the electronic data capture system.

There are several potential flows that would require over-read including spikes or rapid fluctuations in the uroflow curve. These aberrations are commonly caused by mechanical disturbances of the flow sensor and abdominal straining either during or at the end of the void. If the Investigator is of the opinion that the machine read peak flow rate is an artifact and that the peak flow rate should be over-read by applying the 2 second-rule, the Investigator may use standardised methodology.

Detailed over-read procedure will be outlined in the manual of operations (MOP).

10.14.6 Post Void Residual Urine Volume

Following freestanding uroflow, residual urine volume in the bladder shall be assessed by bladder scanner or abdominal ultrasound. Only post void residual urine volume visualised after the valid uroflow shall be used for analyses.

11 Electronic Case Report Form (eCRF) Entry

The Sponsor will provide optional source worksheets in an organised, tabbed binder to facilitate capture of protocol required data. Medical records from Institution and source worksheets will be entered into an online electronic data capture (EDC) system hosted by MedNet, Inc. The EDC System and its eCRFs will be built by the Sponsor and undergo validation and testing prior to launch. Each user will undergo documented training and must be a part of the delegation of authority log. The EDC System requires a personal password that expires every 90 days, automatically logs out after 90 minutes, and since U.S. based, is 21 CFR part 11 compliant. Modifications of data fields will be kept to a minimum, but if an unforeseen error or amendment to protocol demands a change, the system features ability to update in short time.

Data entry should occur in a timely manner for accuracy, but additionally for complying with regulations if unanticipated or serious adverse event occurs. Further, the EDC System will be used by Sponsor to plan monitoring, issue payments, device resupply, and to control the study minimum and maximum enrolment thresholds. See the entry time deadlines per data type below (**Table 8**).

Table 8 eCRF Entry Timely Target

eCRF Data	Entry Time
• Screening Forms and questionnaires	Within 14 Days
• Index Procedure Forms	Within 48 Hours
• Device Performance Issues with clinical sequelae	Within 24 Hours of knowledge of event
• Serious Adverse Event Form (includes Unexpected Adverse Events)	Within 24 hours of knowledge of event
• Subject Death	Within 24 hours of knowledge of event
• Follow-up Forms & questionnaires	Within 14 Days
• Other Forms (Protocol Deviation, etc.)	Within 14 Days

12 Data Collection and Confidentiality

Qualified trial staff at each site will perform primary data collection drawn from source document (hospital chart) review. Sponsor designated monitors will perform clinical monitoring, including review of eCRFs with verification to the source documentation.

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) with regards to the collection, storage, processing and

disclosure of personal information and will uphold the regulation's core principles. This will be completed as follows:

- Personal information will be collected and stored in secure locations at the site
- Participants will be given a site number followed by participant number to ensure data is coded and depersonalized
- Access to the EDC system will be limited
- Data will be transmitted via an EDC system
- Media will redact any personal information before being transferred to Sponsor

13 Risks and Benefits of PUL and the Clinical Investigation

13.1 Anticipated clinical benefits

There are no guaranteed benefits from participation in this study. Extensive clinical experience with the UroLift System, in absence of urinary retention, has established the safety of the procedure and effectiveness of the UroLift System. For those subjects who suffer from acute urinary retention and BPH, the UroLift System has the potential to address their condition without heating, burning, or cutting tissue. The UroLift System has received CE Mark in Europe, allowing it to be marketed to the United Kingdom. In published clinical studies, it has been shown to significantly reduce LUTS rapidly while preserving important functions, such as sexual function and continence.

Because the PUL procedure takes a prostatic tissue sparing approach rather than tissue resection or ablation, there are potential benefits over conventional surgical treatments for BPH. There is a potential that the PUL procedure requires less anaesthesia and causes less bleeding and sexual dysfunction than more invasive modalities such as transurethral resection of the prostate (TURP) or laser resection. There is a potential that there may be a decrease in procedure time, catheter time, and/or post-operative recovery time when compared to other surgical therapies. There is potential that the time waiting for a procedure while catheterised is reduced. Information gained from this study may be used to benefit future subjects and help guide their therapy.

13.2 Anticipated Adverse Events

Adverse events will be solicited from the subject and documented after enrolment (see section 14 Adverse Events) the UroLift System Treatment, and at each follow-up time point. The risks of the undergoing the PUL procedure as part of this study are the same as having the procedure without being in the study.

Possible anticipated adverse events may be, but are not limited to those symptoms or events related to the disease process, the procedure (Section 13.3), device use (Section 13.5), reactions to medication inclusive of anaesthesia, and/or the study testing.

Anticipated adverse events that are: (1) reflective of the disease process (such as exacerbation of LUTS) and/or (2) inherent to this and any prostatic invasive procedure and expected to occur in this subject population are still to be reported as AEs during this study.

13.3 Anticipated Procedural Adverse Events

Possible anticipated complications related to procedure, anaesthesia and medication include, but are not limited to: death, damage to non-urinary systems, surgical trauma, bleeding, catheter misplacement, allergic reaction, decrease in kidney function, pulmonary embolism and infection.

13.4 Protocol Required Testing with Anticipated Adverse Events

Possible anticipated adverse events related to urodynamic testing are discomfort passing urine, urgency, frequency, bladder spasms, lower urinary tract symptoms, haematuria, and urinary tract infection.

13.5 UroLift System Adverse Events

Possible adverse events related to UroLift PUL[27] include but are not limited to:

Adverse tissue reaction or allergic response
Bleeding associated with the urinary tract, gastrointestinal tract, pelvic region or abdomen
Change in urine control muscle function or narrowing of the urine path
Changes in ejaculation such as semen going into the bladder rather than out the end of the penis (retrograde ejaculation), inability to ejaculate (anejaculation), reduced ejaculation volume, delayed ejaculation, change in ejaculate characteristics, blood in semen (hematospermia), and pain with ejaculation
Cloudy urine, discharge, bleeding (haematuria), proteinuria, or blood clots in urine that may require a catheterisation with or without fluid irrigation of the to bladder and urethra (bladder irrigation or evacuation)
Equipment malfunction or device failure such as broken needle or device associated with undesirable clinical sequelae
Elevated PSA
Foreign body in patient and associated problems including foreign body sensation, erosion, inflammation, or irritation

[27] Complications listed in this section were identified through Sponsor risk management files and include both reported and theoretical risks; the majority of AEs reported through Sponsor's clinical studies were mild or moderate and transient in nature (See Sections 5.1.2. and 5.2)

Embolization of foreign body or blood clot
Gastrointestinal (GI) damage or changes including rectal damage, blockage or narrowing in rectum, fistula creation, hemorrhoid creation, hemorrhoidal pain, bleeding from the GI tract, constipation, diarrhea, vomiting, inability to control bowel movements (rectal incontinence), and additional procedure.
Improperly placed implant, including those that are not removable
Inability to urinate requiring a catheter be put in (urinary retention requiring a catheter)
Increased, returned, or failure to improve lower urinary tract symptoms
Having to urinate several times at night (nocturia)
Hypotension or hypertension
Weak urine stream
Sudden urge to urinate (urgency)
Frequency of having to urinate
Urinating small amounts
Straining to urinate
Spraying of urine when going the bathroom, splitting of urinary stream
Difficulty starting or continuing to urinate (urinary hesitancy/ intermittency)
Sensation of not emptying bladder, feeling of incomplete emptying
Incomplete emptying of bladder, increased residual urine
Dribbling after urination
Infection such as urinary tract infection (bacterial colonisation, leukocyturia, sepsis), epididymitis, orchitis, and prostatitis
Stones (calculi) or encrustation on the implant or in the prostate, bladder or other parts of the urinary tract
Pain or discomfort during urination (dysuria)
Pain, tenderness, discomfort, spasms, or burning sensation in areas such as the lower abdomen, back, penis, prostate, scrotum, groin, perineum, urinary tract, bladder or pelvic region associated with undesirable clinical sequelae
Urine leakage (incontinence)
Urinary tract irritation, inflammation, edema, swelling, change in function and compromised function (including kidney, ureter, bladder, prostate, urethra, and penis)
Prostate abnormalities and damage
Puncture of, problems with, injury or damage to the urinary system, bladder, ureter, ureteral orifice, trigone, bladder neck, urethra, or nearby structures including but not limited to false passageway creation, blockage, trabeculation, stricture, adhesion, stenosis, contracture, reduced sensation, spasm and requirement of additional procedure or medication.
Puncture, injury or damage to nerves or neurovascular bundles resulting in foreign body response, erectile dysfunction, pain, reduced sensation, or requirement of additional procedure or medication.
Prostate, bladder, urinary tract or GI tract hyperplasia, dysplasia, neoplasia or polyp formation
Pyrexia
Reproductive system disturbances such as infertility, decreased potency, impotence, erectile dysfunction, pain with erection, penile damage, penile disorder, penile numbness, decrease or loss of sexual desire (libido), loss of orgasm
Requirement for delayed, aborted, changed or additional procedure

13.6 Possible Interactions with Concomitant Medical Treatments

There are no anticipated interactions with concomitant medical treatments. It is recommended that the subject is cleared to discontinue anticoagulant therapy for a period of at least three days prior to surgical intervention unless subject is on maintenance dose of aspirin (≤100mg).

13.7 Possible Risks of Participation in a Clinical Trial

There are standard risks of participating in a research study given potential of accidental disclosure of subject's confidential information. Every effort will be made to ensure that subject personal information remains confidential at all times including application of Subject ID and redacting personal information before submitting to Sponsor.

13.8 Risk Mitigation

Clinical risks will be minimised by careful assessment of the subject prior to, during, and after the procedure. Careful follow-up will help minimise risks associated with changing conditions of the subject. Proper subject selection will be achieved by following the subject inclusion and exclusion criteria. Participating Investigators are highly experienced UroLift operators and experienced in clinical research. The study centres have adequate resources and facilities to safely conduct study with compliance.

The UroLift System itself has safety features. The delivery device can't be deployed without switching the safety trigger off and features a bypass suture cutting mechanism. Users are able to manually retract needle if necessary. All of these features are detailed in the instructions for use.

13.9 Risk-to-Benefit Rationale

The UroLift System is CE marked for use in the United Kingdom. The potential clinical risks in subjects with acute urinary retention have been minimised through the selection criteria for appropriate subjects, experienced investigators (minimum of 30 PUL and seasoned researchers), and prior pre-clinical and clinical testing of the UroLift® System. The analysis shows that the potential subject benefits outweigh the potential risks to the subject. This study will be conducted ethically and in adherence to regulations.

The design of the feasibility study is qualitative, yet with the rigorous data point collection and reasonable sample size, it is expected to provide clinically meaningful information. The goals are twofold, the first to assess initial effectiveness and safety; the

second, to optimise the study design for a larger, significantly powered, randomised trial. The first goal will be supported by the primary endpoint, which is the most accepted surrogate for effective retention resolution. The follow-up schedule is also comprehensive, with five visits through 1 year to gauge the related safety profile, and, the maintenance of voiding without catheter. The benefit of offering UroLift as an alternative option to invasive surgery may be recognised with the comparison to the matched dataset of invasive treatment. The potential for optimising future study design and conduct is increased by including multiple sites, each experienced in UroLift and clinical research, which service a large BPH population.

14 Adverse Events

The following definition is from the ISO 14155 standard.

An adverse event (AE) is defined as any undesirable medical occurrence in a clinical trial subject, whether it is considered to be related to the device or not, that includes a clinical sign, symptom, or condition.

14.1 Serious Adverse Events

Serious Adverse Event (SAE) is defined as untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or

(f) is otherwise considered medically significant by the investigator.

(in-patient hospitalisation is at least 24 consecutive hours)

14.2 Unexpected Adverse Event

An unexpected adverse event is an event which by nature, incidence, severity or outcome has not been identified in the current version of the Sponsor risk management files.

14.3 Not an Adverse Event

Any reoccurrence of urinary retention will not be considered an adverse event, but clot retention that may lead to urinary retention will be considered an adverse event.

Any colonization of subjects requiring catheter deemed not clinically significant will not be considered an adverse event.

The need for any alternative procedure is not considered an AE or SAE, however the diagnosis or symptoms that led to repeat procedure could be. If the alternative procedure involves either (a) hospitalisation greater or equal to 24 hours *longer* than the timeframe that is standard of care for that procedure at that site, or (b) an unexpected outcome then it will be recorded as an SAE.

14.4 Adverse Event Assessment

Any AE experienced after the first UroLift device is introduced (enrolment) will require reporting on the eCRF. In general, a primary diagnosis for the event should be reported instead of each symptom, with the exception of LUTS. Lower urinary tract symptoms should be reported individually per the elements of IPSS. Only exacerbated conditions or new onset qualify as an AE, but if patient history is in question, report AE conservatively.

Adverse events will be summarised by overall adverse events (AEs), severe AEs (grade 3 or higher on CTCAE scale (See **Table 11**), AEs related to device and/or procedure (See **Table 9**), serious adverse events (SAEs) and SAEs related to device and/or procedure. Adverse events will be coded using MedDRA and Common Terminology Criteria for Adverse Events (CTCAE)[28] severity grades and will be presented by System Organ Class (SOC) and preferred term.

Principal Investigators will be responsible for assessing severity via the CTCAE scale (**Table 11**Table 10) and Relatedness (**Table 9**).

Table 9 Device and Procedure Relatedness Definitions

• Highly probable -- The AE follows a reasonable temporal sequence from receipt (or attempted receipt) of the device treatment or procedure.
• Probable -- The AE follows a reasonable temporal sequence from receipt of the device treatment or procedure and the possibilities of factors other than the device treatment or procedure, such as underlying disease, concomitant drugs, or concurrent treatment can be excluded.

[28] National Cancer Institute, Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009; NIH publication # 09-7473. The reprint of the terminology will be part of manual of operations (MOP).

- Possible -- The AE follows a reasonable temporal sequence from receipt of the device treatment or procedure and the possibility of device treatment or procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.
- Unlikely -- The AE has an improbably temporal sequence from receipt of the device treatment or procedure, or it can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.
- Not related -- The AE has no temporal sequence from receipt of the device treatment or procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment

14.5 Adverse Event Reporting

Adverse events will be collected on all enroled subjects. Subjects will be asked about adverse events at each visit, and all AEs will be documented and reported regardless of relatedness.

Adverse events will be documented on the AE electronic case report form (eCRF) within the study's Electronic Data Capture System (EDC).

When an SAE occurs, the Sponsor should be notified within 24 hours of site awareness via completion of the AE eCRF in the EDC System. Sponsor will receive an alert upon any SAE entry and will be responsible for reporting to notified body, ethics committee and all other participating investigators as applicable. Should Sponsor determine, either through investigator reports or in-house testing, that a unexpected SAE presents an unreasonable risk to all participating subjects, Sponsor will suspend the clinical investigation.

It is the responsibility of the Chief Principal Investigator to report all related and unexpected Serious Adverse Events (SAEs) to the ethics committee. The Sponsor may report on behalf of the Chief Investigator. Device-related SAEs in this study, using a CE-marked device in a post-market surveillance study, are reportable to the MHRA Adverse Incident Centre as reported under the requirements of the Devices Vigilance requirement.

Annual and final reports will be provided to the EC as applicable per EC requirements with Sponsor assistance.

14.6 Adverse Event Independent Reviewer

An independent reviewer will be employed for safety review. The independent reviewer will provide comprehensive medical review and adjudicate the reported adverse events. The assessments of the independent reviewer will help to ensure that the adverse event data is accurate, free of bias, and consistently reported across the participating study centres. This independent reviewer will be an independent urologist, with no ties to Sponsor or any of the participating ECs or third party providers. A Safety Plan that describes the adjudication conventions will be established. The independent reviewer will review events, with the support of redacted source documents, to determine AE/SAE/UAE classification, event relatedness, degree of relatedness, event severity, and MedDRA coding. Adjudication will occur ongoing throughout the study and to be completed in advance of the study final report.

Adverse Events with onset within 90 days of Index Procedure will evaluated by independent reviewer per the Clavien-Dindo (CD) classification (**Table 10**).

The independent reviewer may also categorize by CTCAE classification (**Table 11**). Complications, outside the recovery course, will be assigned a CD grade.

Table 10 Clavien Dindo Classification of Surgical Complications (Daniel Dindo, 2004)

Complication Definition	Unexpected events not intrinsic to the procedure (PI to assign grade), should be aligned with the AE relatedness assessment with probably or high probably related to procedure and/or device.
Sequelae Definition	Inherent events to the procedure (will not be assessed further). Example being mild haemaeturia that resolves without treatment.
Grade Level for Complications	**Description**
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications (e.g. change in antibiotics), blood transfusions and total parenteral nutrition.
III	Requiring surgical, endoscopic or radiological intervention
IIIa	Intervention not under general anaesthesia
IIIb	Intervention under general anaesthesia
IV	Life –threatening complication (including CNS complications)* requiring IC/ICU management
Iva	Single organ dysfunction (including dialysis)
IVb	Multi-organ dysfunction
V	Death of a patient
Suffix “d”**	If the patient suffers from a complication at the time of discharge, the suffix d (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.
** For purposes of this study Suffix “d” will not be used.

Table 11 Common Terminology Criteria for Adverse Events Definition

Grade	Guidance
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or non-invasive intervention indicated;

Grade	Guidance
	Limiting age-appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self- care ADL*.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE
*Activities of Daily Living (ADL)	
Instrumental ADL	Refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
Self-care ADL	Refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.7 Device Malfunctions, Failures, or Near Incidents

All device failures or malfunctions will be documented on the appropriate case report form and reported to Sponsor within 24 hours of occurrence. The malfunctioning device involved in the incident will be returned to Sponsor for evaluation, as available. Any unexpected Serious Adverse Event (SAE) occurring as a result of device deficiencies will be reported to the Competent Authorities in accordance with the European Medical Devices directives (93/42/EEC) and all applicable national regulations.

Refer to the manual of operations (MOP) for device return to Sponsor instructions.

15 Study Procedures – Retrospective Cohort

The retrospective chart review will provide a dataset for comparison to specific outcomes in the UroLift cohort. The target population for this arm is BPH patients that presented with AR and went on to de novo invasive surgery from June 1, 2015 to December 31, 2015. Baseline health status through 12 months post-procedure will be collected for those patients meeting criteria.

15.1 Qualifications for Case Abstractors

Case abstractors will be qualified by education or experience to abstract protocol-required information from the medical records; these qualifications will be documented. Case abstractors will be delegated by the Principal Investigator and trained prior to conducting study-specific activities.

15.2 Subject Identification

Case abstractors will create a Master List of all invasive BPH surgeries (TURP, HoLEP, etc.) performed by the site from June 1, 2015 to December 31, 2015. Each case will be reviewed against the study selection criteria (See Section 15.3) and case abstractors will document enrolment status for each subject and the reason(s) for that decision. Patients meeting criteria will be contacted for consent.

15.3 Modified Enrolment Criteria for Retrospective Arm

15.3.1 Retrospective Inclusion Criteria

Patients enroled in this study must meet the following criteria:

1. Male gender
2. Diagnosis of symptomatic BPH
3. Age ≥ 50 years
4. Presented with acute urinary retention with at least one failed trial without catheter prior to invasive surgery (index procedure)
5. Underwent invasive BPH surgery (TURP, HoLEP, etc.) while in retention and performed by site between June 01, 2015 and December 31, 2015.
6. Prostate volume ≤ 100 cc as measured by ultrasound, specimen (tissue) weight, or other standard method for prostate evaluation

15.3.2 Retrospective Exclusion Criteria

Patients will be excluded from the study if any of the following conditions apply.

1. Underwent known BPH surgery prior to the AR and index procedure
2. History of neurogenic or atonic bladder
3. Acute renal failure
4. History of prostate or bladder cancer prior to index procedure
5. Known coagulopathies or subject on anticoagulants within 3 days of index procedure (excluding up to 100mg ASA)
6. Known bladder stones within 3 months of index procedure

7. Known prostatitis requiring treatment (antibiotics) within year prior to index procedure

8. Unable or unwilling to provide informed consent

15.4 Enrolment Procedures- Retrospective arm

A retrospective patient is considered enroled in the clinical study if his records meet inclusion and exclusion criteria and has provided proper consent. Once subject is enroled, data will be extracted from the medical chart and entered into the study EDC.

15.5 Patient Informed Consent – Retrospective arm

A consent form specific to the retrospective arm will be utilised to inform patient of the study, the chart review process and that Sponsor representatives and government bodies may access personal information. If consent is denied, or the patient is no longer reachable, the enrolment log will record reason, and no further data will be collected or retained. At least three attempts, using multiple methods, should be used to contact potentially eligible patients, at the discretion of the PI.

15.6 Subject Withdrawal Procedure – Retrospective arm

Any subject who has provided consent may elect to withdraw their consent. The reason for withdrawal will be recorded, and their data will be excluded.

15.7 Mitigating potential sources of error

There are many sources of bias in retrospective series; therefore, a checklist of potential biases along with proposed solutions was created to aid in the design of this study (**Table 12**). The checklist is based on the work of Kaji et al,[29] Gilbert et al[30] and Walker and Nowacki.[31]

[29] Kaji AH, Schriger D, Green S. Looking through the retrospectoscope: reducing bias in emergency medicine chart review studies. Ann Emerg Med. 2014 Sep;64(3):292-8. doi: 10.1016/j.annemergmed.2014.03.025. Epub 2014 Apr 18. And http://lifeinthefastlane.com/ccc/retrospective-studies-chart-reviews/

[30] Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta DC, Steiner J. Chart reviews in emergency medicine research: Where are the methods? Ann Emerg Med. 1996 Mar;27(3):305-8. PubMed PMID:8599488.

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Table 12 Retrospective Chart Review Design Quality Checklist

Issue and Suggested Solution	Study Design
Chart Review Inappropriate for Study Question	
• Establish whether necessary information is available in the chart. • Define outcome variables to be collected a priori. • Establish if there are sufficient charts to perform the analysis with adequate precision.	• Participating sites are research centres, two sites have presented their own UroLift datasets at medical conferences. • The EDC system (host of the eCRFs) and source worksheets will guide the abstractor on exact data collection requirements. • Participating PIs were qualified due to their high number of BPH patients they treat.
Investigator Conflict of Interest or Bias	
• Declare any conflict of interest. • Provide evidence of Ethics Committee approval. • Submit the data collection form, as well as the coding rules and definitions.	• Financial Disclosure and conflict of interest forms will be completed by all Principal Investigators. • A regulatory binder will be maintained for HRA and EC correspondence including approval materials. • Study will utilise EDC with eCRF completion instructions. MedDRA coding will be used and embedded in the EDC.
Patient Sample is Non-Representative	
• Case selection or exclusion using explicit protocols and well described the criteria. • Ensure all available charts have an equal chance of selection.	• Study design requires that all surgeries during a set amount of time are evaluated for inclusion, and criteria are well matched to the prospective investigation. • The NHS trust system is consistent across centres.
Chart Abstraction is Not Systematic (Misclassification Bias)	
• Use standardised abstraction forms to guide data collection • Provide precise definitions of variables • Pilot test the abstraction form	• EDC will be used with training, written guidelines. • The EDC has been used extensively by Sponsor and can be modified with minimal time and sacrifice to study.
Presence of Missing or Conflicting Data	
• Ensure uniform handling of data that is conflicting, ambiguous, missing, or unknown • Perform a sensitivity analysis if needed	• Handling of missing data for endpoint evaluation is described a priori in clinical protocol
Abstractors Biased or Not Blinded	
• Blind chart reviewers to the etiologic relation being studied or the hypotheses being tested.	• All data will be abstracted. Blinding is not applicable.
Abstractors Not Sufficiently Trained	
• Train chart abstractors. • Describe the qualifications and training of the chart abstracters.	• Abstractor training process will include collaborative review of mock medical chart and EDC entry to test environment.

Issue and Suggested Solution	Study Design
• Ideally, train abstractors before the study starts, using a set of "practice" medical records. • Ensure uniform training, especially in multi-centre studies	• CV of individual(s) will be evaluated.
Abstractors not sufficiently monitored	
• Monitor the performance of the chart abstractors • Hold periodic meetings with chart abstractors and study coordinators to resolve disputes and review coding rules.	• NeoTract will monitor and audit on a periodic basis 100% source verification • A written monitoring plan will be established prior to study commencement and revision controlled throughout the study. • Newsletters will be issued and RC meetings will be held
Chart Abstraction Unreliable	
• A second reviewer should re-abstract a sample of charts, blinded to the information obtained by the first correlation reviewer. • Report a kappa-statistic, intra-class coefficient, or other measure of agreement to assess inter-rater reliability of the data • Provide justification for the criteria for each variable	• Sites will audited according to an a priori audit plan prior to finalisation of data sets • Analysis of inter-rater reliability of the data may be conducted • Study variables are derived from clinical investigations and used for consistency between the study arms.
Sources of Error from the Use of Electronic Medical Records	
• The use of boilerplates, items copied and pasted, default tick boxes and delays in time stamps relative to actual care.	• Manual data entry will be required and EDC designed to prohibit serial data entry. • A customised source documentation plan for each site utilising their medical record systems will be developed.

15.8 Case Abstraction: Data Collection

15.8.1 Screening

The following medical history parameters will be collected from time when patient presented with AR.

• Inclusion/Exclusion confirmation	• Prostate volume (cc) by ultrasound or other methods	• History of BPH: length of time, symptom scores, treatments sought	• Catheterisation and TWOC history
• Co-morbidities	• Uroflowmetry/PVR within 6 months prior to intervention	• IPSS within 6 months prior to intervention	• Other GU treatments

15.8.2 Procedure

The following will be collected (if available):

• Date, duration	• Type of facility, type of surgery	• Complications, adverse events (urological, sexual function, cancer and SAEs)	• Duration of hospital stay
• Catheterisation	• Pathology (documentation only)		

15.8.3 Post-procedure

The following post-surgery data will be collected for period after discharge through 12 months after their surgical intervention (if available):

• Date of contacts	• Type, reason of contact (phone, office visit)	• Complications, adverse events (urological, sexual function, cancer and SAEs)	• Interventions
• BPH medications, indication	• Symptom scores	• Uroflowmetry/PVR	• Catheterisations

16 Study Data Analysis

All effectiveness analyses will be performed on the "intent-to-treat (ITT)" group. All subjects who were enroled with at least one UroLift device introduced will be included in the intention to treat analysis. Effectiveness assessments for enroled subjects whom later undergo surgical retreatment with either PUL or with any other surgical procedure will be censored the day after the secondary intervention. Censoring in adverse event analysis will be applied only to alternative surgical retreatments and not to secondary PUL.

16.1 Interim Safety and Conduct Assessment

This feasibility study is the first to study patients undergoing PUL with AR. As such, the study progress will be assessed formally after the enrolment of the first 15 subjects. The TWOC success rate will be evaluated, as will the enrolment rate, screen failure reasons, related SAEs, and protocol compliance. In the event changes to protocol are warranted, enrolment may be paused until a protocol amendment or informed consent form is approved by HRA. If it is determined that the early success rate is unacceptable, the study may be terminated.

16.2 Per Protocol Population

The PP analysis population is a subset of the ITT population which excludes subjects who do not receive any implants or who have significant violations that impact the study data integrity.

16.3 Safety Population

The safety population will be used for all safety assessments. The safety population includes all enroled subjects with at least one UroLift device introduced. Safety assessments for enroled subjects whom later undergo surgical retreatment with any other surgical procedure will be censored on the day of the secondary intervention. Censoring in adverse event analysis will be applied only to alternative surgical retreatments and not to secondary PUL.

16.4 Missing Data

To protect the scientific integrity and validity of study, a robust data retention plan will be employed through 12 months and reasons for missing data or early exit will be collected. No imputation for missing data points is planned.

16.5 Analysis of Success Measures

Primary Study Assessment:

TWOC is a binary measure of success. The percent of subjects who have a successful TWOC at the 3 day post procedure visit will be presented. Secondary assessments will include the catheter free rate at 1 month along with time without catheter. This primary study assessment will be calculated for both the ITT and the PP analysis populations.

16.6 Additional Assessments

Continuous measures will be summarised by visit. Summary statistics will include the available sample size, mean and standard deviation. Changes from baseline to each follow-up visit will also be calculated and the summary statistics will include the number of patients with change score available, mean, median, standard deviation, and confidence intervals (CI). These assessments will be calculated for both the ITT and PP analysis populations.

The Kaplan-Meier method will be used to calculate freedom from alternative secondary surgery over time and freedom from medical treatment, from the time of the PUL procedure for the ITT and PP populations. Subjects that do not have an alternative procedure will be censored at their last recorded follow-up visit. The probability of freedom from urinary retention will be analysed in a similar manner for the safety population. Time without catheter will be analysed using the Kaplan-Meier method in the ITT and PP populations.

Adverse events will be summarised by overall adverse events (AEs), severe AEs (grade 3 or higher on CTCAE scale), AEs related to device and/or procedure, serious adverse events (SAEs) and SAEs related to device and/or procedure. Adverse events will be coded using MedDRA and CTCAE v4.0 severity grades and will be presented by System Organ Class (SOC) and preferred term. Adverse events will be summarised for the safety population.

Retrospective Arm

The following baseline and procedural data points will be summarised for both the retrospective and the prospective arms. Although the study is not powered to make comparisons between the retrospective surgical patients and the prospective Urolift subjects, comparisons in the observed data will be made statistically. Continuous variables will be compared using a t-test or non-parametric alternative, binary data points will be compared using chi-square or Fisher's exact test.

1) Baseline demographics

2) Duration of catheterisation to procedure (days)
3) Procedure time
4) Hospitalisation time

The following outcomes post procedure will be summarised for the retrospective surgical group and will compared to the results obtained in the prospective study. The statistical significance of any observed differences will be assessed.

1) Total numbers of related AE, SAE, and Clavien-Dindo ≥IIb individually
2) Percent procedure/device related AE rates by month post index procedure and by severity
3) Retreatment post index intervention by time to event and by month
4) Medical treatment post index intervention by time to event and by month
5) Urinary retention recurrence rates at 1 month, 6 weeks and at 3, 6 and 12 months
6) Post-procedure TWOC success percent
7) Catheterisation use

16.7 Evaluation of Study Success

There is no formal study success criteria for this feasibility study. The results will be used to evaluate for a future controlled study of the device in the treatment of urinary retention.

17 Roles and Responsibilities: Sponsor and Investigator

17.1 Sponsor Responsibilities

As the study Sponsor, NeoTract, Inc. has the overall responsibility for the conduct of the study, including assurance that the study meets the local regulatory requirements.

17.2 Investigator and Site Personnel Training

Investigators responsible for treating subjects with the UroLift System have expert experience with the device. A proctoring of the first case will be performed by a NeoTract representative to ensure proper data collection.

The training of appropriate clinical site personnel to the study will also be the responsibility of Sponsor. The Investigator is responsible for ensuring that his/her staff conduct the study according to the protocol and are qualified to perform their delegated study activities. To ensure uniform data collection, adherence to Sponsor procedures and

protocol understanding Sponsor will present a formal training session to study site personnel before study recruitment commences. During this training, navigation of EDC, source documents, protocol, mock retrospective entry, recruitment methods, and consenting documentation will be reviewed. The training will be documented and kept in study files.

17.3 Monitoring Responsibilities

A responsibility of the Sponsor is to ensure proper monitoring of study. Qualified Sponsor clinical monitors will perform on site auditing of study records to ensure accuracy and compliance. A monitoring plan will be established in advance and will include conventions of: essential document compliance, ensuring EC approval is obtained prior to initiating the study, investigators understand and comply with the protocol, all subject consent forms are properly completed, electronic Case Report Forms (eCRFs) are accurate and supported by appropriate source documents (100% review), and all reports are filed in accordance with the study protocol and the appropriate regulations. Additional site visits will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits.

The investigator and study staff are expected to cooperate and provide all relevant study documentation to the monitor upon request, including access to the study data, such as electronic or paper medical records.

If a monitor finds that an investigator is not complying with the executed study agreements, the study protocol, Government regulations, or the requirements of the reviewing EC, prompt action will be taken to secure compliance. Clinical monitors may also be responsible for reviewing the adequacy of the facilities, training, and technical support.

Monitoring visits will be conducted by representatives of Sponsor, qualified monitors, ICH Guidelines for GCP (E6). By signing this study protocol, the Investigator grants permission to Sponsor, and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

17.4 Patient Informed Consent Form (PICF) Template Approval

The Sponsor will provide the recommended and approved subject informed consent form template. This informed consent document complies with applicable regulatory guidelines (ISO 14155-2011 and the Declaration of Helsinki, Good Clinical Practices, GDPR). The overseeing ethics committee (EC) may alter or amend the text as appropriate, but the

Sponsor must approve the final text of the informed consent before subject enrolment can begin.

17.5 Investigator Responsibilities

The investigator is responsible for ensuring the study is conducted according to all signed agreements, the study protocol, country and local regulations and Good Clinical Practice requirements. Investigators will be trained on the appropriate records to maintain and reports to file. Sponsor and investigators will maintain records relating to the clinical investigation for a period of two years after study termination or as required by local and national regulations. No investigator may dispose of any of these records until receipt of written notification to do so from Sponsor.

- Investigators are required to maintain the following records:
    - Subject reports including signed informed consent and case report forms.
    - Sponsor notification of SAEs (sponsor to be notified within 24 hours of knowledge of event)
    - Correspondence with HRA, NHS, EC, Sponsor, and any other study entity related to this study including with Co-Investigators.
    - The protocol, protocol amendments and documentation (date and reason) for each deviation from the protocol.
- Investigator reports include:
    - Unexpected serious adverse events – must be reported to Sponsor within 24 hours of awareness. The Chief PI is responsible to report to the EC per EC requirements.
    - Subject Death – must be reported to NeoTract, Inc. within 24 hours of site's knowledge of event even if unrelated.
    - Withdrawal of EC approval – must be reported to Sponsor within 5 working days.
    - Annual Progress Reports– must be submitted to Sponsor, the monitor, and the EC at regular intervals, within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
    - Deviations from the protocol – submit to Sponsor as soon as possible, but no later than 5 working days, submit reports of serious breaches per guidelines to appropriate authorities.
    - Final report – submit to Sponsor and the EC within 1 year after termination or completion of the study.

- Records shall be maintained by the Investigators for (1) a period of 2 years after trial is terminated or completed, or (2) in accordance with applicable country regulations, whichever is longer.

The investigators have been selected because of their medical qualifications, interest in participation, ability to conduct and document the results of the study, ability to accrue subjects, experience in treating subjects with BPH and acute urinary retention, and experience performing PUL procedures.

All investigators will provide their curriculum vitae to Sponsor and sign an investigator agreement. Investigator completion of financial disclosure forms will be required.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information before inclusion in the study using the EC approved informed consent document, including the objective and procedures of the study and the possible risks involved. Informed consent will be obtained prior to performing any study-related procedures, including screening procedures and any washout of medications as applicable.

In cases of withdrawal or lost to follow up, the study Investigator should document the contact attempts and reasons for subject withdrawal or loss to follow up with other supporting information as requested on the appropriate eCRFs.

17.6 Approval to Recruit -Ethics Committee Review and Compliance

The Investigator will submit the study protocol and Patient Informed Consent Form (PICF) to the local hospital trial administration and obtain the proper approval before being allowed to conduct and participate in this study.

The Sponsor will submit the study protocol and Patient Informed Consent Form (PICF) and supporting materials to REC and HRA via the IRAS system. The PICF will be in compliance with requirements of the Declaration of Helsinki and Good Clinical Practice. The investigator will be responsible for fulfilling any conditions of approval imposed by the human research ethics committee, such as regular reporting, study timing, etc. The Investigator will provide the Sponsor with copies of such approvals and reports.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements.

Sponsor will submit any change to the study protocol to the HRA and EC for review and approval before implementation.

18 Device Use and Ancillary Equipment

The Sponsor will provide UroLift System devices for enrolment free of charge. These devices will be shipped from a European subsidiary throughout enrolment. Any opened devices will be documented along with its lot number. After enrolment completes, unused devices will be returned. The study device box will have a unique sticker to distinguish from the facility commercial supply. Investigators will ensure the devices allocated for the study are stored securely and separately from commercial inventory. Should the facility not have available the required ancillary equipment, Sponsor will loan UroLift compatible equipment sets for the duration of enrolment.

19 Potential Device Changes

No device changes are anticipated for this study.

20 Termination of Study

The study will be terminated after the following milestones have been met; a) all active subjects have completed their 12 month study visit and b) completion of the final study report and c) study centres are closed. Investigators will be notified by Sponsor of study termination for any other reason.

21 Early Study Centre Termination

Sponsor reserves the right to terminate participation in this study for any of the following reasons:

- Failure to secure Informed Consent from a subject or legal representative prior to enroling the subject into this study.
- Repeated protocol deviations which would affect primary study assessment evaluation or data integrity.
- Repeated failure to complete case report forms within the timeframe agreed to in this protocol.
- Repeated failure to collect and provide source documentation to support CRF entry.
- Failure to report serious adverse events on a timely basis.
- Inability to enrol a subject within 2 months of EC & R&D approval

22 Study Protocol Amendments

Any amendment to the study protocol will be written by Sponsor. Amendments cannot be implemented without prior written EC approval except as necessary to eliminate immediate safety hazards to subjects. A documented training of amendments will be conducted. An amendment intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the ECs are given expedited notification.

Any amendments that impact the PICF will also require EC approval along with informing the subject and signature on the updated form.

PROTOCOL REVISION HISTORY

Protocol Revision	Revision Date	History
A	30 May 17	Initial Release
B	31 Jan 18	1. Replaced unanticipated with unexpected adverse event throughout. 2. Clarified SAE reporting requirements 3. Replaced CEC with an Independent Safety reviewer. 4. Revised TWOC endpoint to 300 ml PVR. 5. Updated to note urodynamics testing may be performed at each study site if a testing facility is available and a qualified operator is on-site 6. Removed urodynamics and Active UTI from eligibility procedures 7. Clarified language surrounding procedure antibiotics 8. Clarified UA and urine culture requirements. 9. Removed Active Urinary Tract Infection and active gross hematuria from exclusion criteria 10. Removed reference to IPP size for inclusion for prospective arm 11. Revised exclusion criteria language for prospective arm: #5, #10 and #11 12. Revised inclusion criteria for retrospective arm: excl. #5 and #6 13. Revised exclusion criteria for retrospective arm: #3, #5 and added #8. 14. For retrospective arm, updated to include all site invasive BPH surgeries. 15. Removed reference to protocol deviation waivers & over-read for enrolment. 16. Removed refresher training
C	12 August 2018	1. Removed symptom questionnaire requirements at screening.

Protocol Revision	Revision Date	History
		2. Removed questionnaire and UA requirements at post-procedure. 3. SHIM only required at baseline and follow-up if subject is sexually active. 4. Defined treatment failure, alternative procedure and secondary PUL criteria. 5. Urine cultures only required if UA is abnormal, CS and indicates a urinary infection. Required uploads for abnormal UAs and urine cultures. 6. Removed 125ml minimum voided volume for uroflows at follow-up. 7. Removed requirement to discontinue alpha blockers on day of index procedure. 8. Removed requirement for ultrasound uploads. 9. Revised require case requirements for PIs from 50 to 30. 10. Expanded re-catheter rate assessment to 1 month. Added re-catheter assessment to secondary assessments and removed from primary study assessment. 11. Only AEs related to cancer, LUTs, SAEs and sexual function are required to be collected in the Retrospective arm. 12. Revised 4 centres to 6 centres 13. removed the word transrectal to include ultrasound as a method to evaluate prostate size. 14. Defined symptoms not considered an adverse event. 15. Minor risk revisions
D	14 Dec 2018	1. Admin change on Protocol Signature Page: removed duplicate Sponsor signature 2. Admin change on Table 7: removed Urine C&S "if indicated" at 6 months. This was a typo. A UA is not required. 3. Increased sample size to up to 55 subjects

23 Publication Policy

At the conclusion of the study, a manuscript may be prepared for publication in a scientific journal. Publication of any study results, including any public presentation of data in abstract form, will be prepared using data retrieved from the study database and only with prior notification to Sponsor.