Lewis, A. L., Young, G. J., Abrams, P., Blair, P. S., Chapple, C., Glazener, C. M. A., Horwood, J., McGrath, J. S., Noble, S., Taylor, G. T., Ito, H., Belal, M., Davies, M. C., Dickinson, A. J., Foley, C. L., Foley, S., Fulford, S., Gammal, M. M., Garthwaite, M., ... Drake, M. J. (2019). Clinical and Patient-reported Outcome Measures in Men Referred for Consideration of Surgery to Treat Lower Urinary Tract Symptoms: Baseline Results and Diagnostic Findings of the Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM). *European Urology Focus*, *5*(3), 340-350. https://doi.org/10.1016/j.euf.2019.04.006

Peer reviewed version

Link to published version (if available):
10.1016/j.euf.2019.04.006

Clinical and patient reported outcome measures in men referred for consideration of surgery to treat LUTS: baseline results and diagnostic findings of the UPSTREAM trial

*Amanda L. Lewis[1,2], *Grace J. Young[1,2], Paul Abrams[3], Peter S. Blair[1,2], Christopher Chapple[4], Cathryn M.A. Glazener[5], Jeremy Horwood[1,2], John S. McGrath[6], Sian Noble[7], Gordon T. Taylor[8], Hiroki Ito[3], Mohammed Belal[9], Melissa C. Davies[10], Andrew J. Dickinson[11], Charlotte L. Foley[12], Steve Foley[13], Simon Fulford[14], Mohsen M. Gammal[15], Mary Garthwaite[14], Mark R.E. Harris[16], Petre C. Ilie[17], Robert Jones[18], Samer Sabbagh[19], Robert G. Mason[20], Ester McLarty[11], Vibhash Mishra[21], Jaswant Mom[22], Roland Morley[23], Salvatore Natale[11], Tharani Nitkunan[24], Tobias Page[25], David Payne[26], Tina G. Rashid[23], Kasra Saeb-Parsy[27], Sarb S. Sandhu[28], Adrian Simoes[29], Gurpreet Singh[15], Mark Sullivan[30], Heidi V. Tempest[30], Srinivasa Viswanath[31], Roger M.H. Walker[24], J. Athene Lane[1,2], Marcus J. Drake[3].

**Lewis and Young contributed equally to the paper*

[1]Bristol Randomised Trials Collaboration (BRTC), Bristol Trials Centre, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK

[2]Population Health Sciences, Bristol Medical School, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK

[3]Bristol Urological Institute, Level 3, Learning and Research Building, North Bristol NHS Trust, Southmead Hospital, Bristol BS10 5NB, UK

[4]Sheffield Teaching Hospitals NHS Trust, Room H26, H-Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK

[5]Health Services Research Unit, University of Aberdeen, 3rd Floor, Health Sciences Building, Foresterhill, Aberdeen, Scotland, AB25 2ZD, UK

[6]University of Exeter Medical School, St. Luke's Campus, Heavitree Road, Exeter, EX1 2LU, UK

[7]Population Health Sciences, Bristol Medical School, University of Bristol, 1-5 Whiteladies Road, BS8 1NU, UK

[8]University of Plymouth, Plymouth, Devon PL4 8AA, UK

[9]University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, Edgbaston, Birmingham, B15 2GW, UK

[10]Salisbury NHS Foundation Trust, Salisbury District Hospital, Odstock Road, Salisbury, Wiltshire, SP2 9BJ, UK

[11]Plymouth Hospitals NHS Trust, Derriford Hospital, Plymouth, PL6 8DH, UK

[12]East and North Hertfordshire NHS Trust, Urology Department, Ashwell Block, Lister Hospital, Coreys Mill Lane, Stevenage, Hertfordshire, SG1 4AB, UK

[13]Royal Berkshire NHS Foundation Trust, Royal Berkshire Hospital, London Road, Reading, Berkshire, RG1 5AN, UK

[14]South Tees Hospitals NHS Foundation Trust, James Cook University Hospital, Marton Road, Middlesbrough, TS4 3BW, UK

[15]Southport and Ormskirk Hospital NHS Trust, Town Lane, Kew, Southport, Merseyside, PR8 6PN, UK

[16]University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO16 6YD, UK

[17]The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust, Gayton Road, King's Lynn, PE30 4ET, UK

[18]Taunton and Somerset NHS Foundation Trust, Musgrove Park Hospital, Urology Department, Taunton, Somerset, TA1 5DA, UK

[19]St George's University Hospitals NHS Foundation Trust, Blackshaw Road, Tooting, London, SW17 0QT, UK

[20]Torbay and South Devon NHS Foundation Trust, Torbay Hospital, Lowes Bridge, Torquay, TQ2 7AA, UK

[21]Royal Free London NHS Foundation Trust, Royal Free Hospital, Pond Street, London, NW3 2QG, UK

[22]North Cumbria University Hospitals NHS Trust, West Cumberland Hospital, Hensingham, Whitehaven, Cumbria, CA28 8JG, UK

[23]Imperial College Healthcare NHS Trust, Charing Cross Hospital, Fulham Palace Road, W6 8RF, UK

[24]Epsom and St Helier University Hospitals NHS Trust, Wrythe Lane, Carshalton, Surrey, SM5 1AA, UK

[25]The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, High Heaton, Newcastle Upon Tyne, NE7 7DN, UK

[26]Kettering General Hospital NHS Foundation Trust, Rothwell Road, Kettering, Northants, NN16 8UZ, UK

[27]Urology Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, CB2 0QQ, UK

[28]Kingston Hospital NHS Foundation Trust, Surrey, KT2 7QB, UK

[29]East Kent Hospitals University NHS Foundation Trust, Kent and Canterbury Hospital, Ethelbert Road, Canterbury, Kent, CT1 3NG, UK

[30]Nuffield Department of Surgical Sciences, Oxford University and Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Old Road, Headington, Oxford, OX4 7LE, UK

[31]Royal Liverpool and Broadgreen University Hospitals NHS Trust, Prescot Street, Liverpool, L7 8XP, UK

Amanda L. Lewis, PhD	Email: amanda.lewis@bristol.ac.uk
Grace J. Young, MSc	Email: grace.young@bristol.ac.uk
Paul Abrams, MD, FRCS(Urol)	Email: paul.abrams@bui.ac.uk
Peter S. Blair, PhD	Email: p.s.blair@bristol.ac.uk
Christopher Chapple, MD, FRCS(Urol), FEBU	Email: c.r.chapple@sheffield.ac.uk
Cathryn M.A. Glazener, MB ChB, MD, PhD, FRCOG	Email: c.glazener@abdn.ac.uk
Jeremy Horwood, PhD	Email: j.horwood@bristol.ac.uk
John S. McGrath, BM, BS, MD, FRCS(Urol)	Email: john.mcgrath4@nhs.net
Sian Noble, PhD	Email: s.m.noble@bristol.ac.uk
Gordon T. Taylor, PhD	Email: anythingyoulike@btinternet.com
Hiroki Ito, PhD	Email: pug.daikichi@gmail.com
Mohammed Belal, MA MB BChir FRCS(Urol)	Email: mohammed.belal@uhb.nhs.uk
Melissa C. Davies, MD, FRCS(Urol)	Email: melissa.davies@salisbury.nhs.uk
Andrew J. Dickinson, MBBS, FRCSEd, MD, FRCS(Urol)	Email: andrew.dickinson1@nhs.net
Charlotte L. Foley, BMBCh MD(Res) FRCS(Urol)	Email: charlotte.foley@nhs.net
Steve Foley, FRCS(Urol)	Email: steve.foley@fit2live.me.uk
Simon Fulford, MBBS FRCS(Eng) FRCS(Urol)	Email: simonfulford@nhs.net
Mohsen M. Gammal, FRCS(Urol)	Email: gammal53@hotmail.com
Mary Garthwaite, MBBS, PhD, FRCS(Urol)	Email: mary.garthwaite@nhs.net
Mark R. E. Harris, MB, ChB, FRCS(Urol), MD	Email: mark.harris@uhs.nhs.uk
Petre C. Ilie, MD, PhD, FEBU, FRCS(Urol), MBA	Email: PETRE.ILIE@nnuh.nhs.uk

Robert Jones, BMedSci BMBS RCSEd Email: robert.jones@tst.nhs.uk

Samer Sabbagh, MD, MRCS(Ed), FEBU, CABU, FRCS(Urol) Email: samer.katmawisabbagh@stgeorges.nhs.uk

Robert G. Mason, MBBS, FRCSGlas, FRCS(Urol) Email: robert.mason@nhs.net

Ester McLarty, MB, ChB, MSc, FRCS(Urol) Email: emclarty@nhs.net

Vibhash Mishra, MBBS, MS, FRCSEd, FRCS(Urol) Email: vibhashmishra@nhs.net

Jaswant Mom, MBBS, MS, LRCP, MRCS, FRCS(Urol) Email: Jaswant.Mom@ncuh.nhs.uk

Roland Morley, MB, BS, FRCS(Urol) Email: rolandmorley@nhs.net

Salvatore Natale, MD, FRCS(Urol), FEBU Email: Salvatore.natale@phnt.swest.nhs.uk

Tharani Nitkunan, PhD, FRCS(Urol) Email: tharaninitkunan@nhs.net

Tobias Page, MBBS, BSc, PhD, MRCS, FRCS(Urol) Email: toby.page@nuth.nhs.uk

David Payne, MB, ChB, BSc, FRCS(Urol) Email: david.payne4@nhs.net

Tina G. Rashid, MBBS(Lon) FRCS(Urol) Email: tina.rashid1@nhs.net

Kasra Saeb-Parsy, BSc, MB BS, FRCSEd(Urol) Email: kasra.saeb-parsy@nhs.net

Sarb S Sandhu, BSc MD FRCS(Urol) Email: sarbjinder.sandhu@nhs.net

Adrian Simoes, MBBS, MS, FRCS(Urol) Email: adrian.simoes@nhs.net

Gurpreet Singh, MBBS, FRCSEd, FRCS(Urol) Email: gurpreet.singh@nhs.net

Mark Sullivan, MB, BS, MD, FRCS(Urol) Email: mark.sullivan@ouh.nhs.uk

Heidi V. Tempest, MA, MD, FRCS(Urol) Email: heidi.tempest@ouh.nhs.uk

Srinivasa Viswanath, MBBS, FRCSEd, FRCSI, FRCS(Urol) Email: Srinivasa.Viswanath@rlbuht.nhs.uk

Roger M.H. Walker, FRCS(Urol), FEBU Email: roger.walker@nhs.net

J. Athene Lane, PhD Email: athene.lane@bristol.ac.uk

Marcus J. Drake^, MA, DM, FRCS(Urol)

^Corresponding author

Email: marcus.drake@bui.ac.uk

Telephone: +44 117 955050

Address: University of Bristol and Bristol Urological Institute, Level 3, Learning and Research Building, North Bristol NHS Trust, Southmead Hospital, Bristol BS10 5NB, UK.

Keywords: Benign prostatic obstruction, Bladder outlet obstruction, Detrusor overactivity, Detrusor underactivity, Lower urinary tract symptoms, Patient reported outcome measures, Prostate, Surgery, Underactive bladder, Urodynamics.

Word count – abstract: 298

Word count – text: 2728

Abstract

Background: Clinical evaluation of male lower urinary tract symptoms (MLUTS) in secondary care uses a range of assessments. It is unknown how MLUTS evaluation influences outcome of therapy recommendations and choice, notably urodynamics (UDS; filling cystometry and pressure flow studies).

Objective: Report the participant sociodemographic and clinical characteristics, and initial diagnostic findings of the Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM). UPSTREAM is a randomised controlled trial evaluating whether symptoms are non-inferior and surgery rates are lower if UDS is included.

Design, Setting, and Participants: 820 men (≥18-years) seeking treatment for bothersome LUTS recruited from 26 NHS hospital urology departments.

Intervention: Care pathway based on routine, non-invasive tests (control) or routine care plus UDS (intervention arm).

Outcome Measurements: Primary outcome is International Prostate Symptom Score (IPSS) and key secondary outcome is surgery rates, 18-months after randomisation. International Consultation on Incontinence Questionnaires (ICIQ) were captured for MLUTS, sexual function and UDS satisfaction.

Statistical Analysis: Baseline clinical and patient reported outcomes (PROMs), and UDS findings, were informally compared between arms. Trends across age groups for urinary and sexual PROMs were evaluated with a Cuzick's test and questionnaire items compared using Pearson's correlation coefficient.

Results and Limitations: Storage LUTS, notably nocturia, and impaired sexual function are prominent in men being assessed for surgery. Sociodemographic and clinical evaluations were similar between arms. Overall mean IPSS and quality of life scores were 18.94 and

4.13, respectively. Trends were found across age groups, with older men suffering from higher rates of incontinence, nocturia and erectile dysfunction and younger men suffering from increased daytime frequency and voiding symptoms. Men undergoing UDS expressed high satisfaction with the procedure.

Conclusions: Men being considered for surgery have additional clinical features that may affect treatment decision-making and outcomes, notably storage LUTS and impaired sexual function.

Patient Summary: We describe initial assessment findings from a large clinical study of the treatment pathway for men suffering with bothersome urinary symptoms referred to hospital for further treatment, potentially including surgery. We report the patient characteristics and diagnostic test results, including symptom questionnaires, bladder diaries, flow rate tests and urodynamics.

1. Introduction

Male lower urinary tract symptoms (MLUTS) are common; the prevalence increases with age, they can have detrimental impact on quality of life (QoL), and are associated with considerable personal and societal costs [1-4]. Various causative mechanisms can contribute, so proper assessment is needed to aid diagnosis and guide treatment decision-making. Benign prostate enlargement (BPE), causing partial bladder outlet obstruction (BOO), can cause voiding LUTS (slow stream, hesitancy, straining) and post-voiding LUTS (post-micturition dribble (PMD) and sensation of incomplete emptying). In such cases prostate surgery, such as a transurethral resection of the prostate (TURP), is commonly considered. Another cause of voiding LUTS, however, is declining strength of the bladder (detrusor underactivity; DU), where prostate surgery is unlikely to improve symptoms [5]

and would expose men to associated risks (e.g. sexual side effects or incontinence). This is, however, an area where inconsistent findings have been reported [6, 7]. Co-existing storage LUTS (urgency, increased daytime voiding frequency, urgency incontinence and nocturia), including overactive bladder syndrome (OAB) also do not improve reliably after surgery to relieve BOO [8]. Nocturia is further complicated by behavioural and systemic factors influencing urine production, and giving rise to nocturnal polyuria (NP) [9]. Since any combination of BOO, DU, OAB and NP can be present in a given individual, accurate assessment is essential.

Typically, men with LUTS should undergo the following 'routine' assessments: (1) medical history to establish which LUTS are present and their QoL impact, relevant comorbidities, medications and lifestyle, sexual function and the man's perspectives regarding LUTS and treatment options; (2) bladder diary (≥3-days); (3) validated symptom score questionnaires; (4) urinalysis; (5) digital rectal examination (DRE); and (6) uroflowmetry (maximum flow rate (Q_{max}), voided volume (VV) and post void residual (PVR)) [10, 11].

Invasive urodynamics (UDS) is the only test, however, able to distinguish between BOO and DU, by finding slow Q_{max} with abnormal increase or reduction of detrusor pressure respectively, as expressed by the BOO Index (BOOI) and Bladder Contractility Index (BCI). UDS also identifies storage phase dysfunction, notably detrusor overactivity (DO). A high BOOI (>40) with a normal BCI (>100) and absence of DO seemingly represent the most suitable UDS features to consider surgery for BOO. However, literature reviews over the last decade identified there is no robust, high-level clinical evidence to support use of UDS routinely (as opposed to selectively) for MLUTS [11-13]. Thus, UDS is generally used as an 'optional' test in UK practice, at the discretion of the responsible clinician.

UPSTREAM is a randomised controlled trial (RCT) in the context of the care pathway from urological presentation with LUTS to outcome of therapy [14], using the full set of routine assessments, and randomising half of the participants to additional assessment with UDS. The study's main outcomes will be reported in 2019, and are expected to have significant implications for the management of LUTS in secondary care. Here, we report baseline characteristics and the initial diagnostic testing outcomes for the study.

2. Material (Patients) and Methods

2.1. Study design and participants

Details of background and design are published elsewhere [14, 15]. In brief, UPSTREAM is a two-arm, multicentre RCT, that randomised eligible men between care pathways using routine care with UDS or without it. The design was utilised to establish non-inferiority in symptom severity 18-months after randomisation [15]. The primary outcome is International Prostate Symptom Score (IPSS) at 18-months, and the key secondary outcome is the influence of UDS on rates of bladder outlet surgery. The setting is urology departments of 26 National Health Service (NHS) hospitals throughout England. Men (≥18-years) seeking further treatment for bothersome LUTS, which may include surgery were invited to participate. Men were excluded if they required a catheter to pass urine, had a relevant neurological disease, were undergoing treatment for prostate or bladder cancer, had previously had prostate surgery, were medically unfit for surgery, and/or were unwilling to be randomised or comply with trial requirements. The study also assesses cost-effectiveness and includes detailed qualitative research [16].

2.2. Trial registration and ethics

The study was registered with the ISRCTN registry, 8 April 2014 (ISRCTN56164274). The National Research Ethics Service Committee South Central – Oxford B reviewed and approved the study, 10 July 2014 (reference 14/SC/0237).

2.3. Outcome measures

Data collection occurred between October 2014 and August 2018. Outcome measures, including components and timings, are detailed elsewhere [14, 15].

2.3.1. Sociodemographic and clinical outcomes

Sociodemographic characteristics (e.g. age, ethnicity, and postal code (i.e. geographical identifier) and clinical outcomes (e.g. comorbidities, DRE, uroflowmetry, UDS and additional tests) were collected via case report forms completed by trained hospital (centre) staff. Key clinical outcomes were followed up at subsequent appointments through to 18-months after randomisation [14]. For all men who underwent UDS, filling cystometry and pressure flow voiding data were collected. Procedures of UDS testing and quality control assessment were as stated in the International Continence Society Standards [14].

2.3.2. Patient-reported outcome measures (PROMS)

PROMS captured at 0- (baseline), 6-, 12- and 18-months included the IPSS [17], International Consultation on Incontinence Questionnaire for MLUTS (ICIQ-MLUTS) and associated sexual matters (ICIQ-MLUTSsex) (see Supplementary Material 1). ICIQ 3-day bladder diaries were completed at baseline and 18-months. Men who underwent UDS were asked to complete the ICIQ-UDS-Satisfaction questionnaire. Copies of ICIQ materials can be requested via the website: www.iciq.net [18].

2.4. Statistical analysis

The database was locked prior to final data analysis, as described elsewhere [15]. Data presented are n (%) or mean (standard deviation (SD)) unless otherwise stated. Any missing baseline data is due to missing/incomplete questionnaires, and men who withdrew fully from the study. Baseline characteristics were considered imbalanced if they met a pre-specified absolute difference of 10% or 0.5 SDs between arms. Measurements taken at UDS have been separated by arm, as some patients deviated from their initial randomised allocation. However, no formal comparisons were made between the arms.

For exploratory baseline analysis, urinary and sexual symptoms were compared across age categories (<55, 55-64, 65-74, ≥75-years) using logistic regression and Cuzick's test for trend. Categorical outcomes were dichotomised for ease of reporting and to aid interpretation. As seen in previous studies [19], to aid clinical interpretation, daytime frequency was broken down into ≤8 times per day versus >8 times per day, and men were considered to have nocturia if they were getting up to urinate more than once per night. Sexual function was considered impaired if a man scored one or more for any of the four symptom questions in the ICIQ-MLUTSsex PROM. When comparing the IPSS and ICIQ questions, a Pearson's correlation coefficient was calculated along with its associated p-value. Analyses were performed using STATA 15.1 [20].

3. Results

3.1. Recruitment

Supplementary Material 2 details recruitment to the study, including assessment for eligibility (screening) data. Between October 2014 and December 2016, 8671 patient

referrals and notes were scrutinised to identify suitable men to invite to take part in the study; 5910 (68%) were considered ineligible and reasons for non-inclusion were unidentified for 1279 (15%). Of the 1482 (17%) considered eligible, 820 (55%) were randomised (enrolled; 427 in the UDS arm and 393 in the routine care arm) and 662 (45%) declined to take part (see Supplementary Material 2).

3.2. Sociodemographic and clinical characteristics

Table 1 reports the study baseline sociodemographics. Men were predominantly of white ethnicity (92%) with a median social deprivation index score of 14 (range from 0-78; full range of scale 0-100). Median age was 68-years, with an interquartile range (IQR) of 62-74 and overall range of 22-91. Many patients (67%) had comorbidities at baseline; 27% (215/803) had one comorbidity, 19% (156/803) two and 21% (170/803) more than two. Table 2 reports the baseline clinical characteristics and PROMS. Approximately 78% of the cohort had a benign enlargement based on DRE findings. Although 70% did not have additional discretionary tests at baseline, common additional procedures were PSA testing (14%) and cystoscopy (9%). The median Q_{max} was 10.8 ml/s (IQR 7.6-15.0), PVR 100 ml (IQR 44-182) and VV 214 ml (IQR 143-316).

3.3. Patient reported outcome measures (PROMs)

3.3.1. QoL, urinary symptoms, sexual function and bladder diaries

Mean IPSSs were 18.52 and 19.39 for the UDS and routine care arms, respectively. The median IPSS QoL score was four (mean=4.13), which corresponds to ‘mostly dissatisfied’ on the scale of delighted (zero) – terrible (six).

Almost half of the cohort were urinating more than eight times per day, on average. Nocturia prevalence was high, with 78% of men getting up to urinate more than once per night. Completion of baseline ICIQ-MLUTSsex was ~90%, and 67% percent of men reported that urinary symptoms were affecting their sex life. Only 26% could achieve an erection with normal rigidity and only 20% had a normal quantity of ejaculation. All urinary and sexual symptoms were well balanced at baseline with a maximum absolute difference of 5% or 0.2 SDs between arms. The median time between baseline questionnaire completion and randomisation was 0-days (IQR range 0, 0), but for 38 men, baseline questionnaires were completed outside a six month window from the randomisation date. Completion of all three days on the bladder diaries was relatively poor (~25%) but, of those fully completed, data was balanced between arms. Supplementary Material 3 presents an overview of baseline bladder diary completion rates.

3.3.2. Symptoms by age group

There was a strong association of age group with almost all symptoms (Table 3). Sexual symptoms concerning quality of erections/ejaculations were much worse for older men. Fifty percent of men aged <55-years suffered from reduced erections compared with 93% of ≥75-year olds, with a similar difference for reduced ejaculation. Using the ICIQ-MLUTS questionnaire we found that younger age groups had higher voiding scores ($p<0.001$) whereas older age groups suffered from higher incontinence scores (generally reflecting storage LUTS rather than actual incontinence) ($p=0.003$). For urinary frequency, getting up to urinate more than once per night (nocturia) was higher in older men whereas daytime frequency (>8-times) was higher in younger men. Overall IPSS and QoL was slightly better

(lower) for older age groups but statistical evidence was limited. For individual symptoms, urgency and strength of stream were similar across age groups.

3.3.3. Cross-checking IPSS with ICIQ-MLUTS

Comparing responses of the IPSS questionnaire with the equivalent ICIQ-MLUTS questions, all answers were highly correlated ($p<0.001$) (Table 4). Nocturia had the highest correlation coefficient ($r=0.86$); however, 141/770 (18%) of the respondents gave conflicting answers, despite similarity of the two items. Daytime frequency had the lowest correlation coefficient ($r=0.44$). Storage symptoms were more bothersome than voiding symptoms, measured using the ICIQ-MLUTS questionnaire. The most bothersome symptoms were nocturia and urgency, with mean scores of 5.85 and 5.78, respectively, out of ten. Completion rates for the PROMs were 93-96%. Completion of the ICIQ-MLUTS questions related to individual symptom bother was generally good (88-94%) but lower than the corresponding questions on symptom severity.

3.3.4. UDS satisfaction

The ICIQ-UDS-Satisfaction questionnaire identified the median satisfaction score to be ten out of ten, indicating very high overall satisfaction with UDS assessment (Table 5). Data was also obtained from 28 men in the routine care arm who underwent UDS. Fifty percent of men scored the test to be better than expected, and conversely 26% said it was worse than expected. Generally, components of the UDS evaluation were scored very favourably, although 11% reported dissatisfaction with the explanation of the results.

3.4. UDS data

The number allocated to receive UDS was 427, with 353 (83%) actually doing so. The number allocated to routine care was 393, however, 28 (7%) of these men went on to receive UDS. Further details on the reasons for deviating from assigned allocation can be found in Supplementary Material 2. The median BOOI and BCI for the UDS arm were 48 and 112 respectively. For those initially allocated to non-UDS but who received UDS, BOOI was 55 and BCI was 114 (Table 6). DO was seen in 52% of men in the UDS arm and 64% of men in the non-UDS arm.

4. Discussion

This large secondary care dataset (820 men across 26 secondary care urology centres) provides a unique insight into MLUTS, and study results will address an identified lack of robust evidence for impact of UDS assessment on outcome [11-13]. The overall level of symptom severity on IPSS was 18.94, which is slightly low compared with studies of surgical interventions, probably because the study baseline is taken from the start of the secondary care diagnostic pathway, rather than at the time of intervention. For example, the range of mean baseline IPSSs from four surgery meta-analyses were 15.80 to 27.90 [21-24].

The target population is men being assessed to decide whether surgery would be suitable. Many men solely reported storage LUTS, or described them as the main source of bother. This reflects everyday reality of referral, but is a concern since outcomes of surgery to treat BOO are less reliable where storage LUTS are problematic [25]. In particular, nocturia was highly prevalent and bothersome (IPSS, ICIQ-MLUTS and bladder diary), yet nocturia often reflects systemic conditions unrelated to LUTS [9]. Consequently, evaluations must identify where systemic factors could be relevant; the only test that would identify it in standard LUTS pathways is the bladder diary (by discerning a high nocturnal polyuria index), yet we

found that only 25% fully completed all days and nights of a 3-day diary, even under the optimal conditions of a well-supported clinical trial. Supporting data presents a real-life experience of how difficult it is to persuade people to complete bladder diaries. As with storage LUTS, the issue of sexual function needs to be discussed, as identified in EAU Guidelines [10], and observing that impaired sexual function affects two thirds of men at baseline shows how the issue is pertinent.

Of those considered eligible, 55% agreed to take part, similar to our previous studies [26]. Completion rates for PROMs were good, including 94% full completion at baseline of the IPSS. By including the ICIQ-MLUTS questionnaire we captured symptoms not measured by IPSS (notably PMD and incontinence), and the bother caused by individual symptoms. This showed that the two PROMs perform differently, with some items generating rather different results for equivalent components, notably increased daytime voiding frequency. Future analysis will additionally review bladder diary parameters to corroborate the PROMs reporting and identify which provided a better reflection of the diary findings. We identified where additional 'discretionary' tests were done, with PSA testing (14%) the most common. This value reflects PSA testing done in secondary care, additional to preceding tests done in primary care, which is where most such testing would usually be undertaken. Data on primary care PSA testing was not captured in the study.

There was crossover between arms, with 83% of men randomised to UDS receiving it, and conversely 28 men from the routine care arm undergoing UDS. A variety of reasons for this was identified and, underlying, it is likely a reflection of anxieties and preconceptions experienced by patients and healthcare professionals. In the UDS arm, overall BOOI was 48 (>40 indicates obstruction) and BCI was 112 (>100 is good contractility), with similar results for men in the routine care arm also receiving UDS. Since flow rate findings were very

similar between the arms, and symptoms were likewise well-matched, we hypothesise that UDS characteristics probably would have been similar if they had been measured in the entire routine care arm. Satisfaction with UDS overall was high, and indicates several elements which were explored in previously published qualitative research from the UPSTREAM trial [16].

The UPSTREAM trial will evaluate whether a treatment pathway that includes UDS is non-inferior to the standard (routine care) pathway for men eligible for surgery. It will determine whether UDS should change from being an optional test in routine assessment of male LUTS, and additionally scrutinise the contribution of each diagnostic test in the care pathway. The protocol and analysis plan were published before recruitment end [14, 15]. The dataset is a real-life reflection of referral, but the context means that completion rates for many assessments is higher than everyday clinical experience.

5. Conclusions

UPSTREAM is a large RCT of MLUTS looking at the full pathway of assessment and treatment, randomising between routine care and routine care plus UDS. Arms are well-matched in terms of sociodemographic, baseline and initial test responses. The results presented reflect a real-life population in which storage LUTS and impaired sexual function are prevalent, which are key considerations for men under assessment for potential use of surgery as part of therapy.

Acknowledgements

The authors thank all the men who participated in the UPSTREAM trial. We also thank the participating NHS hospitals (reported elsewhere [14]), in particular the Principal Investigators, Research Nurses, Clinical Trial Assistants, Administrators and all other support staff, for their dedication and hard work. The study would not have been possible without the involvement of patients and the centres, and we are extremely grateful.

We also thank the members of the independent Trial Steering Committee and Data Monitoring Committee, as well as our Trial Management Group (consisting of co-applicants, representatives from the Study Office and patient representatives) for their continued counsel and support.

We are also grateful to Lyndsey Johnson, Samantha Clarke and Kwame Ansu for their contributions as UPSTREAM Lead Research Nurse at different periods throughout the study, and Charlotte McDonald and Aneta Taylor for their administrative support in recent years.

We thank the wider qualitative team members (Lucy Selman, Cynthia Ochieng and Clare Clement) and health economist (Caoimhe Rice) for their substantial input in other areas of the study; design, conduct and analysis.

We wish to acknowledge Professor Rob Pickard, a Consultant Urological Surgeon and co-applicant, who sadly passed away in July 2018. Professor Pickard was a major contributor in developing the original funding application and contributed valuable expertise to study design and oversight.

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 12/140/01). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. This study was designed and delivered in

collaboration with the Bristol Randomised Trials Collaboration (BRTC), a UKCRC Registered Clinical Trials Unit which, as part of the Bristol Trials Centre, is in receipt of NIHR Clinical Trials Unit (CTU) support funding. The UPSTREAM trial was sponsored by North Bristol NHS Trust (NBT). Study data were collected and managed using REDCap (Research Electronic Data Capture, Harris PA, et al. J Biomed Inform. 2009 Apr;42(2):377-81) hosted at the University of Bristol.

Conflict of Interests / Financial Disclosures

The authors declare the following: Paul Abrams reports being a consultant for Astellas and Ipsen and a speaker for Astellas, Pfizer and Sun Pharma. He was also a co-applicant of the UPSTREAM trial, thus received grant funding. Peter Blair reports being a co-applicant of the UPSTREAM trial, thus received grant funding. Chris Chapple reports being an author for Allergan; a grant, scientific study/trial, researcher, author, meeting participant, speaker and consultant/advisor for Astellas Pharma; a consultant/advisor for: Bayer Schering Parma AG, Ferring, Galvani Bioelectronics (GSK), Pierre Fabre, Taris Biomedical, Urovant Sciences and Symimetics, including patent; a researcher and scientific study/trial for Ipsen; and meeting participant and speaker for Pfizer. He was also a co-applicant of the UPSTREAM trial, thus received grant funding. Marcus Drake reports being on associated advisory boards; a speaker (including for Pfizer); an active researcher and grant-holder in this field; and receives non-financial support from Allergan, Astellas, Ferring. He was also chief investigator of the UPSTREAM trial, thus received grant funding. Cathryn Glazener reports being a co-applicant of the UPSTREAM trial, thus received grant funding. Mark Harris reports being a paid speaker for Astellas and Boston Scientific. Jeremy Horwood reports being a co-applicant of the UPSTREAM trial, thus received grant funding. Athene Lane reports being a

co-applicant of the UPSTREAM trial, thus received grant funding. Amanda Lewis reports being funded by the UPSTREAM grant. John McGrath reports being a co-applicant of the UPSTREAM trial, thus received grant funding. Tharani Nitkunan reports being a speaker/receiving financial support from Allergan, Astellas and Contura. Sian Noble reports being a co-applicant of the UPSTREAM trial, thus received grant funding. Gordon Taylor reports being a co-applicant of the UPSTREAM trial, thus received grant funding. Grace Young reports being funded by the UPSTREAM grant. Roger Walker reports receiving educational grants for speaking at meetings from Astellas and Pfizer. Nil else.

All other authors: Nothing to declare.

References

1. Martin, S.A., et al., *Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men.* 2011. **29**(2): p. 179-184.
2. Kupelian, V., et al., *Prevalence of Lower Urinary Tract Symptoms and Effect on Quality of Life in a Racially and Ethnically Diverse Random Sample: The Boston Area Community Health (BACH) Survey.* Archives of Internal Medicine, 2006. **166**(21): p. 2381-2387.
3. Taub, D.A. and J.T.J.C.U.R. Wei, *The economics of benign prostatic hyperplasia and lower urinary tract symptoms in the united states.* 2006. **7**(4): p. 272-281.
4. Coyne, K.S., et al., *The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS.* BJU Int, 2009. **103 Suppl 3**: p. 4-11.
5. Thomas, A.W., et al., *The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up.* 2004. **93**(6): p. 745-750.
6. Han, D.H., et al., *The efficacy of transurethral resection of the prostate in the patients with weak bladder contractility index.* Urology, 2008. **71**(4): p. 657-61.
7. van Venrooij, G.E., H.H. van Melick, and T.A. Boon, *Comparison of outcomes of transurethral prostate resection in urodynamicallyobstructed versus selected urodynamicallyunobstructed or equivocal men.* Urology, 2003. **62**(4): p. 672-6.
8. Housami, F. and P.J.C.U.R. Abrams, *Persistent detrusor overactivity after transurethral resection of the prostate.* 2008. **9**(4): p. 284-290.
9. Drake, M.J., *Should Nocturia Not Be Called a Lower Urinary Tract Symptom?* European Urology, 2015. **67**(2): p. 289-290.
10. Gratzke, C., et al., *EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction.* European Urology, 2015. **67**(6): p. 1099-1109.
11. Jones, C., J. Hill, and C. Chapple, *Management of lower urinary tract symptoms in men: summary of NICE guidance.* BMJ, 2010. **340**: p. c2354.

12. Clement, K.D., et al., *Invasive urodynamic studies for the management of lower urinary tract symptoms (LUTS) in men with voiding dysfunction.* Cochrane Database Syst Rev, 2015. **4**: p. CD011179.
13. Parsons, B.A., et al., *The role of invasive and non-invasive urodynamics in male voiding lower urinary tract symptoms.* World J Urol, 2009. **2**: p. 191-7.
14. Bailey, K., et al., *Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) for diagnosis and management of bladder outlet obstruction in men: study protocol for a randomised controlled trial.* Trials, 2015. **16**: p. 567-567.
15. Young, G.J., et al., *Statistical analysis plan for the Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM).* Trials, 2017. **18**(1): p. 455-455.
16. Selman, L.E., et al., *Recommendations for conducting invasive urodynamics for men with lower urinary tract symptoms: Qualitative interview findings from a large randomized controlled trial (UPSTREAM).* Neurourol Urodyn, 2018(0): p. 1-10.
17. Barry, M.J., et al., *The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association.* J Urol, 1992. **148**(5): p. 1549-57.
18. Bristol Urological Institute. *The International Consultation on Incontinence Questionnaire*. [cited 2019 26 February]; Available from: http://www.iciq.net.
19. Brindle, L.A., et al., *Measuring the psychosocial impact of population-based prostate-specific antigen testing for prostate cancer in the UK.* 2006. **98**(4): p. 777-782.
20. StataCorp, *Stata Statistical Software: Release 15*. 2017: College Station, TX: StataCorp LLC.
21. Perera, M., et al., *Prostatic Urethral Lift Improves Urinary Symptoms and Flow While Preserving Sexual Function for Men with Benign Prostatic Hyperplasia: A Systematic Review and Meta-analysis.* European Urology, 2015. **67**(4): p. 704-713.
22. Zang, Y.-C., et al., *Photoselective vaporization of the prostate with GreenLight 120-W laser versus transurethral resection of the prostate for benign prostatic hyperplasia: a systematic review with meta-analysis of randomized controlled trials.* 2016. **31**(2): p. 235-240.
23. Teng, J., et al., *Photoselective vaporization with the green light laser vs transurethral resection of the prostate for treating benign prostate hyperplasia: a systematic review and meta-analysis.* BJU Int, 2013. **111**(2): p. 312-23.
24. Lee, S.W., et al., *Transurethral Procedures for Lower Urinary Tract Symptoms Resulting From Benign Prostatic Enlargement: A Quality and Meta-Analysis.* Int Neurourol J, 2013. **17**(2): p. 59-66.
25. Choi, H., et al., *Prediction of persistent storage symptoms after transurethral resection of the prostate in patients with benign prostatic enlargement.* Urol Int, 2014. **93**(4): p. 425-30.
26. Glazener, C., et al., *Conservative treatment for urinary incontinence in Men After Prostate Surgery (MAPS): two parallel randomised controlled trials.* Health Technol Assess, 2011. **15**(24): p. 1-290, iii-iv.
27. Manchester Information & Associated Services (MIMAS). *GeoConvert*. [cited 2018 19 October]; Available from: http://geoconvert.mimas.ac.uk/.

Take Home Message

Men being considered for surgery have additional clinical features that may affect treatment decision-making and outcomes, notably storage LUTS and impaired sexual function. Sociodemographic and clinical evaluations were similar between arms. Overall mean IPSS and quality of life scores were 18.94 and 4.13. Men undergoing UDS expressed high satisfaction with the procedure.

Table 1. Baseline sociodemographics of men randomised (enrolled) to the UPSTREAM trial

		Urodynamics		**Routine care**
	n[a]	***Mean (SD)* or n (%)**	**n**[a]	***Mean (SD)* or n (%)**
Total number of participants	427		393	
Age(years)	424	67.51 (9.59)	389	67.81 (8.79)
Hospital (Centre)[b]				
1	427	56 (13%)	393	58 (15%)
2		12 (3%)		20 (5%)
3		35 (8%)		27 (7%)
4		29 (7%)		26 (7%)
5		29 (7%)		18 (5%)
6		5 (1%)		4 (1%)
7		17 (4%)		9 (2%)
8		9 (2%)		12 (3%)
9		17 (4%)		14 (4%)
10		11 (3%)		6 (2%)
11		8 (2%)		7 (2%)
12		16 (4%)		17 (4%)
13		15 (4%)		11 (3%)
14		17 (4%)		19 (5%)
15		14 (3%)		13 (3%)
16		21 (5%)		23 (6%)
17		24 (6%)		13 (3%)
18		14 (3%)		12 (3%)
19		3 (1%)		6 (2%)
20		15 (4%)		16 (4%)
21		13 (3%)		13 (3%)
22		9 (2%)		7 (2%)
23		13 (3%)		21 (5%)
24		10 (2%)		9 (2%)
25		11 (3%)		9 (2%)
26		4 (1%)		3 (1%)
Ethnicity				
White	415	377 (91%)	383	356 (93%)
Black/African/Caribbean/Black British		8 (2%)		6 (2%)
Mixed/Multiple ethnic groups		17 (4%)		11 (3%)
Asian/Asian British		2 (<1%)		1 (<1%)

Other ethnic group		3 (1%)		2 (1%)
Disclosure declined		8 (2%)		7 (2%)
Index of Multiple Deprivation (IMD) scores 2015 (based on postal codes)				
Median IMD score 2015[c]	411	*14 (8, 12)*	383	*14 (8, 24)*
Quintile 1 *(most deprived)*		43 (10%)		61 (16%)
Quintile 2		75 (18%)		49 (13%)
Quintile 3		92 (22%)		91 (24%)
Quintile 4		106 (26%)		86 (22%)
Quintile 5 *(least deprived)*		95 (23%)		96 (25%)

[a]The number of men who we have data for (denominator); three men in the urodynamics arm and four men in the routine care arm requested for all of their data to be withdrawn, therefore the maximum values are 424 and 389 respectively (apart from centre), [b]Centre names have been replaced with numeric identifiers for the purpose of reporting, [c]Higher scores mean higher levels of deprivation (http://geoconvert.mimas.ac.uk) [27]

Table 2. Baseline clinical characteristics of men randomised (enrolled) to the UPSTREAM trial

		Urodynamics		Routine care
	n[a]	*Mean (SD)* or n (%)	n[a]	*Mean (SD)* or n (%)
Clinical baseline characteristics				
Comorbidities at baseline	420	281 (67%)	383	260 (68%)
DRE findings[b]				
No abnormality	395	108 (27%)	375	120 (32%)
Benign enlargement	395	312 (79%)	375	287 (77%)
Suspected prostate cancer	395	16 (4%)	375	8 (2%)
Other	395	22 (6%)	375	20 (5%)
Uroflowmetry[c]				
Maximum flow rate – Q_{max} (ml/s)	402	*10.20 (7.40, 15.00)*	371	*11.00 (7.90, 58.30)*
Post void residual volume – PVR (ml)	401	*100.00 (40.00, 180.00)*	373	*100.00 (45.00, 189.00)*
Voided volume - VV (ml)	405	*215.00 (133.00, 318.00)*	376	*214.00 (149.50, 316.00)*
Additional (discretionary) tests				
PSA test	413	57 (14%)	383	57 (15%)
Cystoscopy		44 (11%)		25 (7%)
Urea & Electrolytes		18 (4%)		17 (4%)
Kidney Ultrasound		14 (3%)		11 (3%)
Voiding urinary cytology		2 (<1%)		2 (1%)
Prostate volume measurement		15 (4%)		7 (2%)
IPSS: Symptom severity at baseline				
Total IPSS	403	*18.52 (6.90)*	371	*19.39 (7.14)*
Incomplete Emptying	411	*2.64 (1.71)*	379	*2.88 (1.72)*
Frequency	411	*3.36 (1.35)*	379	*3.56 (1.30)*
Intermittency	411	*2.58 (1.69)*	379	*2.65 (1.62)*
Urgency	409	*2.60 (1.68)*	379	*2.80 (1.66)*
Weak Stream	409	*3.17 (1.57)*	379	*3.16 (1.61)*
Straining	408	*1.56 (1.56)*	377	*1.67 (1.66)*
Nocturia	410	*2.60 (1.32)*	379	*2.72 (1.28)*
IPSS QoL	411	*4.07 (1.36)*	379	*4.20 (1.25)*
ICIQ MLUTS				
Voiding score[d]	394	*8.88 (4.04)*	370	*9.30 (4.38)*
Incontinence score[e]	395	*5.01 (3.37)*	369	*5.19 (3.27)*
Daytime frequency (>8 times)	398	160 (40%)	374	169 (45%)
Nocturia (>1 times per night)	398	300 (75%)	374	301 (80%)
ICIQ MLUTS – sexual matters				
Erections (reduced or none)	389	277 (71%)	362	275 (76%)
Ejaculation (reduced or none)	383	300 (78%)	359	295 (82%)
Painful ejaculation (Yes)	359	56 (16%)	343	71 (21%)
Urinary symptoms affected sex life?	378	259 (69%)	358	233 (65%)

Continued over page

Bladder Diary[f]				
Voiding frequency (voids per 24-hours)	106	*10.20 (3.37)*	99	*9.65 (2.93)*
Daytime Frequency		*8.38 (2.78)*		*7.87 (2.41)*
Nocturia Frequency		*1.81 (1.26)*		*1.78 (1.13)*
Maximum voided volume (ml)		*334.29 (131.02)*		*344.41 (132.25)*
Mean 24-hour total voided volume (ml)		*1755.96 (628.80)*		*1780.19 (639.13)*
Nocturnal polyuria index (%)		*23.14 (13.20)*		*22.64 (13.07)*

[a]The number of men who we have data for (denominator); three men in the urodynamics arm and four men in the routine care arm requested for all of their data to be withdrawn therefore the maximum values are 424 and 389 respectively (apart from centre), [b]These were not treated as mutually exclusive and centre staff were asked to tick all that applied, the denominator is the number of men who answered yes/no to at least one finding, [c]As data was skewed for these outcomes, medians and IQRs are presented [d]Voiding scale, on a scale of 0-20 with larger scores indicating more severe symptoms, [e]Incontinence scale, on a scale of 0-24 with larger scores indicating more severe symptoms, [f]The number of men who completed all 3-days of the bladder diary.

Table 3. Urinary and sexual symptoms by age in the UPSTREAM trial

Age group (years)	**<55 (N=66)**	**55-64 (N=217)**	**65-74 (N=355)**	**≥75 (N=175)**	**P value**
Urinary and sexual symptoms	*Mean (SD)* /n(%)	*Mean (SD)* /n(%)	*Mean (SD)* /n(%)	*Mean (SD)* /n(%)	
IPSS (min 'n')	**n=58**	**n=209**	**n=342**	**n=165**	
Incomplete emptying	*3.16 (1.53)*	*2.95 (1.82)*	*2.66 (1.68)*	*2.56 (1.69)*	0.003[a]
Frequency	*3.50 (1.31)*	*3.67 (1.30)*	*3.43 (1.32)*	*3.26 (1.38)*	0.010[a]
Intermittency	*2.84 (1.78)*	*2.81 (1.70)*	*2.50 (1.61)*	*2.54 (1.64)*	0.039[a]
Urgency	*2.71 (1.64)*	*2.65 (1.66)*	*2.68 (1.66)*	*2.80 (1.73)*	0.450[a]
Weak stream	*3.02 (1.55)*	*3.31 (1.65)*	*3.09 (1.56)*	*3.18 1.56)*	0.624[a]
Straining	*2.16 (1.81)*	*1.90 (1.75)*	*1.46 (1.45)*	*1.38 (1.58)*	<0.001[a]
Nocturia	*2.24 (1.48)*	*2.45 (1.31)*	*2.69 (1.24)*	*2.97 (1.27)*	<0.001[a]
Total IPSS score	*19.62 (6.62)*	*19.71 (7.57)*	*18.50 (6.87)*	*18.61 (6.71)*	0.090[a]
IPSS QoL	*4.40 (1.36)*	*4.18 (1.32)*	*4.06 (1.32)*	*4.14 (1.27)*	0.189[a]
ICIQ MLUTS (min 'n')	**n=57**	**n=207**	**n=332**	**n=165**	
Voiding score	*10.07 (4.37)*	*9.99 (4.49)*	*8.79 (3.93)*	*8.22 (4.11)*	<0.001[a]
Incontinence score	*4.60 (3.38)*	*4.90 (3.44)*	*5.02 (3.28)*	*5.65 (3.17)*	0.003[a]
Daytime frequency (>8 times)	28 (49%)	109 (52%)	140 (41%)	52 (31%)	<0.001[b]
Nocturia (>1 times)	36 (63%)	151 (72%)	269 (80%)	145 (86%)	<0.001[b]
ICIQ MLUTS – sexual matters (min 'n')	**n=56**	**n=201**	**n=313**	**n=132**	
Erections (reduced or none)	28 (50%)	124 (60%)	253 (77%)	147 (93%)	<0.001[b]
Ejaculation (reduced or none)	30 (54%)	149 (72%)	265 (82%)	151 (96%)	<0.001[b]
Painful ejaculation	15 (27%)	45 (22%)	51 (16%)	16 (12%)	0.003[b]
Urinary symptoms affected sex life?	34 (61%)	155 (75%)	221 (69%)	82 (54%)	0.006[b]

[a]Cuzick's test for trend, [b]Logistic regression, min 'n' refers to the lowest denominator in the category

Table 4. Comparing IPSS and ICIQ MLUTS questionnaires in the UPSTREAM trial

ICIQ			IPSS			Correlation (IPSS vs ICIQ)		ICIQ symptom bother score (0-10)	
N	Question	Scale	N	Question	Scale	N	R (p value)[a]	N	Mean (sd)
768	Do you strain to continue urinating?	Never (0) – All of the time (4)	785	How often have you had to strain to start urination?	Not at all (0) – Almost always (5)	762	0.72 (<0.001)	725	3.70 (3.24)
770	Would you say that the strength of your urinary stream is?	Normal (0) – Reduced all of the time (4)	788	How often have you had a weak urinary stream?	Not at all (0) – Almost always (5)	767	0.73 (<0.001)	759	4.84 (3.13)
772	Do you stop and start more than once while you urinate?	Never (0) – All of the time (4)	790	How often have you found you stopped and started again several times when you urinated?	Not at all (0) – Almost always (5)	771	0.69 (<0.001)	751	4.27 (3.10)
774	How often do you feel that your bladder has not emptied properly after you have urinated?	Never (0) – All of the time (4)	790	How often have you had the sensation of not emptying your bladder completely after you finish urinating?	Not at all (0) – Almost always (5)	773	0.71 (<0.001)	759	5.09 (3.17)
774	Do you have a sudden need to rush to the toilet to urinate?	Never (0) – All of the time (4)	788	How often have you found it difficult to postpone urination?	Not at all (0) – Almost always (5)	771	0.64 (<0.001)	766	5.78 (3.25)
772	How often do you pass urine during the day?	1-6 time (0) – 13 or more times (4)	790	Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	Not at all (0) – Almost always (5)	771	0.44 (<0.001)	762	5.05 (3.38)
772	During the night, how many times do you have to get	None (0) – Four or more (4)	789	How many times did you typically get up to urinate from the time	None (0) – 5 times (5)	770	0.86 (<0.001)[b]	770	5.85 (3.33)

up to urinate, on average?	you went to bed until the time you got up in the morning?		

[a]Pearson correlation coefficient (R) and corresponding p value, [b]Despite being the same question on almost the same scale 141 (18%) of men gave conflicting answers.

Table 5. Satisfaction with urodynamics (UDS)

	n (U:R)	Urodynamics arm n(%)/ *Median(IQR)*	Routine care arm n(%)/ *Median(IQR)*
Number of men who received urodynamics		353	28
ICIQ-UDS-Satisfaction			
Overall satisfaction (0-10)	297:6	*10.00 (9.00, 10.00)*	*10.00 (10.00, 10.00)*
The test was...better than expected	302:6	152 (50%)	3 (50%)
...same as expected		52 (17%)	1 (17%)
...worse than expected		77 (26%)	2 (33%)
...different but no better or worse		21 (7%)	0 (0%)
Did you think the test was successful?[a]	282:5	275 (98%)	5 (100%)
Knowing what you know now, would you take the test? [b]	303:6	294 (97%)	6 (100%)
Satisfaction with information received in the post? [c]	293:6	260 (89%)	6 (100%)
Satisfaction with information from the doctor? [c]	284:6	268 (94%)	6 (100%)
Satisfaction with the doctor? [c]	277:5	274 (99%)	5 (100%)
Satisfaction with the nurse who performed the test? [c]	297:6	294 (99%)	6 (100%)
Was your privacy and dignity preserved? [d]	298:6	294 (99%)	6 (100%)
Satisfaction with the explanation of the results? [e]	293:5	261 (89%)	5 (100%)
Would you recommend the test to friends/family? [f]	301:6	278 (92%)	6 (100%)

U=Urodynamics, R=Routine care, [a]Very, quite, somewhat or a little successful vs. unsuccessful, [b]Definitely or probably vs. not sure, probably or definitely not, [c]Very-little satisfied vs. neutral or dissatisfied, [d]Extremely or moderately preserved vs. a little bit/not at all, [e]Very-little satisfied vs. neutral, dissatisfied or not received, [f]Definitely or probably vs. not sure or not

Table 6. Urodynamic (UDS) assessment findings

		Urodynamics		Routine care
	n[a]	*Mean (SD)* or n (%)	n[a]	*Mean (SD)* or n (%)
Filling cystometry				
Detrusor overactivity	341	179 (52%)	22	14 (64%)
Maximum cystometric capacity (ml)	338	*340.45 (159.72)*	23	*315.61 (143.09)*
Pressure flow study				
Voided volume (ml)	339	*279.91 (144.19)*	23	*257.04 (156.54)*
Maximum flow rate (ml/s)	335	*9.06 (4.77)*	23	*7.71 (3.84)*
Residual urine, in ml, (IQR)[b]	312	*32.00 (0.00, 145.50)*	20	*50.00 (0.00, 127.00)*
Bladder Contractility Index (BCI) [b]	259	*112.00 (89.00, 135.00)*	17	*114.00 (101.00, 121.50)*
Bladder Outlet Obstruction Index (BOOI) [b]	302	*48.10 (29.00, 70.00)*	19	*55.00 (23.00, 102.00)*

[a]The number of men who we have data for (denominator); in the urodynamics arm, we are aware that 353 men received UDS and in the non-UDS arm 28 men received UDS, therefore the maximum values are 353 and 28 respectively, [b]As data was skewed for these outcomes, medians and IQRs are presented

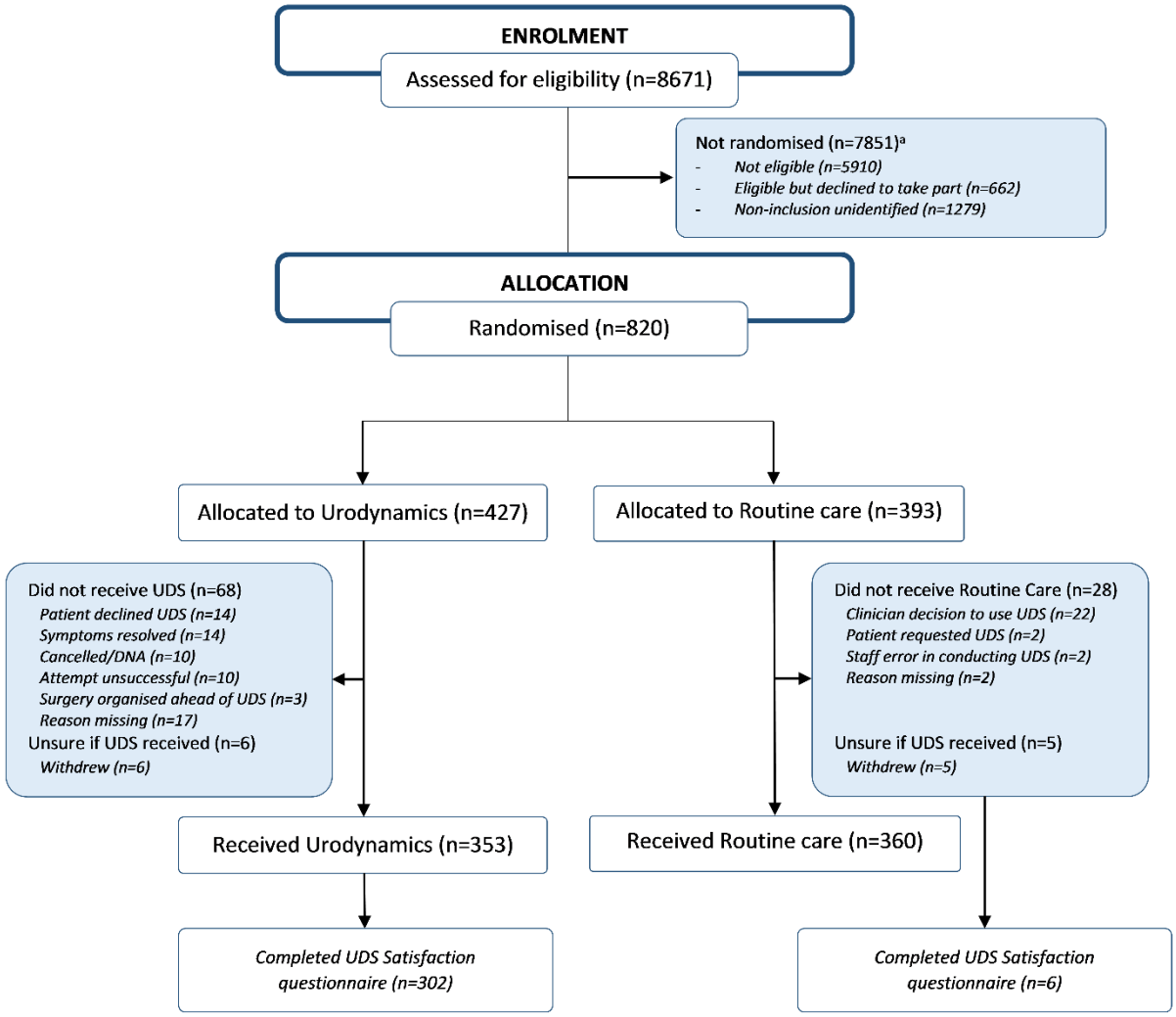
Supplementary Material 1.

Table S1. UPSTREAM urinary symptoms patient reported outcomes completed by participants at 0- (baseline), 6-, 12- and 18-months after randomisation

Questionnaire	Outcome/item(s)	Outcome/scoring system
IPSS: International Prostate Symptom Score [17]	1. Incomplete emptying 2. Frequency 3. Intermittency 4. Urgency 5. Weak stream 6. Straining 7. Nocturia QoL Patient's perceived quality of life	Urinary symptoms (qns 1-7) score: 0 to 35 with a higher score reflecting higher severity (e.g. 1-7 = mild; 8-19 = moderate; and 20-35 = severe). Quality of life (QoL) due to urinary symptoms: score 0 "Delighted" to 6 "Terrible".
ICIQ-MLUTS: International Consultation on Incontinence Modular Questionnaire – Male Lower Urinary Tract Symptoms (see [18])	1. Hesitancy 2. Straining to continue urination 3. Strength of stream 4. Intermittency 5. Incomplete emptying 6. Urgency 7. Urge urinary incontinence 8. Stress urinary incontinence 9. Unexplained urinary incontinence 10. Nocturnal enuresis 11. Post-micturition dribble (PMD) 12. Nocturia 13. Frequency	A voiding and incontinence score were generated, as well as daytime and night-time frequency data; - Voiding scale: 0 to 20 with larger scores indicating more severe symptoms - Incontinence scale: 0 to 24 with larger scores indicating more severe symptoms - Daytime frequency (>8 times per day) - Nocturia (>1 times per night)
ICIQ-MLUTSsex: International Consultation on Incontinence Modular Questionnaire – Male Sexual Matters associated with Lower Urinary Tract Symptoms (see [18])	1. Erections possible 2. Orgasm possible 3. Pain/discomfort during ejaculation 4. Impact or urinary symptoms	Number (%) reported for; - Erections (reduced or none) - Ejaculation (reduced or none) - Painful ejaculation (slight, moderate or severe pain) - Urinary symptoms spoilt sex life? (a little/somewhat/a lot)

Supplementary Material 2.

Figure S2.1. Recruitment and allocation in the UPSTREAM trial



[a]For a summary of reasons why men were ineligible or declined to take part, please refer to Supplementary Material Tables S2.2 and S2.3.

Table S2.1 Overview of screening data

	N	%
Total patients assessed for eligibility across 26 centres:	**8671**	-
Of those patients SCREENED (n=8671):		
Considered ineligible:	5910	68%
Considered eligible:	1482	17%
Reasons for non-inclusion unidentified:	1279	15%
Of those patients considered ELIGIBLE (n=1482):		
Declined to take part:	662	45%
Randomised:	820	55%

Table S2.2. Summary of reasons why men were ineligible to take part (n=5910)

	N 5910	%
Exclusion criteria	***2926***	***50%***
Undergoing treatment/surveillance prostate or bladder cancer	1293	44%
Previous prostate surgery	559	19%
Urinary retention	392	13%
Neurological disease	302	10%
Not willing / able to comply with essential study procedures	208	7%
Not medically fit for surgery	172	6%
Other reasons	***2510***	***42%***
Medical team did not consider patient suitable for research/this study (non-prostatic/non-bothersome LUTS; presentation required additional assessment; recurrent UTIs; unrelated condition)	1068	43%
Further details not provided	714	28%
Patient no longer seeking treatment (or surgery)	346	14%
Already had diagnostic assessments (e.g. UDS) and/or treatment plan is active (e.g. surgery/medication)	341	14%
Considered too young especially for surgery	35	1%
Unable to make further contact with patient – deemed ineligible	6	0%
Reason missing	***474***	***8%***

Table S2.3. Summary of reasons why men who were eligible declined to take part (n=662)

	N 662	%
Reasons	***535***	***81%***
Does not want to be randomised	144	27%
Other commitments	89	17%
Could not decide	79	15%
Number of visits	76	14%
Not interested in research studies	56	10%
Does not want urodynamics or additional tests	41	8%
Other health issues more important	29	5%
Number of questionnaires	16	3%
Transport / parking issues	3	1%
Relocating	2	0%
Reason missing	***127***	***19%***

Supplementary Material 3.

Figure S3.1. Overview of ICIQ 3-day bladder diary completion rates within the UPSTREAM trial at baseline.