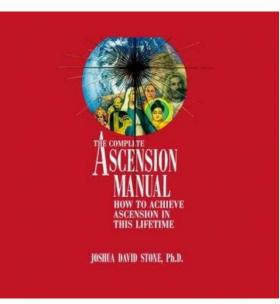
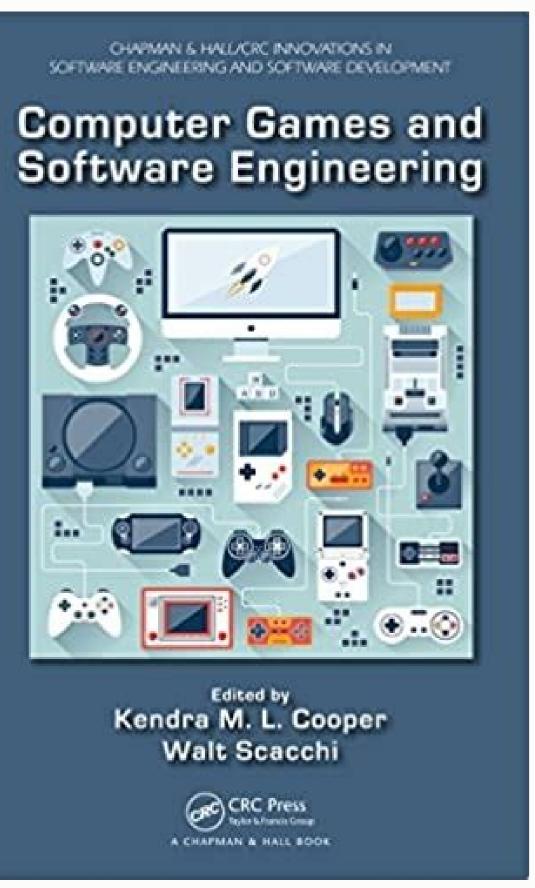
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Men undergoing surgery will also attend clinic for flow rate testing 4 months after operation. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. SponsorNBT will act as the Sponsor for this trial. These include:

In the include of the outlet channel pergardless of whether BPO is price in this prove universet in the surgical procedure will be offset in some men due to deterioration in storage LUTS (e.g. incontinence, overactive bladder) We therefore anticipate the overall IPSS at 18 months in both arms of price in surgery rates. However, to ensure that the men in the urodynamic arm are not disadvantaged by the reduction in surgery rates, we need to ensure that the primary outcome, symptom score, has adequate power to rule out non-inferiority. Randomisation will be stratified by centre. BlindingBlinding in the urodynamic unit is not possible nor appropriate in this pragmatic trial, given that men are only catheterised in the involve group allocation cannot be concealed from the man or the staff. If the patient has changed his mind, however, and no longer experts procedures specified on the form. This will be adapted for dissemination through public channels. In addition, the PMG will also meet at the Trial Steering Committee meetings. Therefore, at the request of the TSC, we revised the accrual projections based on a more realistic assumption conditioned both on differential recruitment by centres over time and recruitment capacity. Subsequently, a further internal feasibility phase was conducted between February and April 2015 with a revised target of 42 participants from 4 centres, with additional reporting to the STC upon conclusion of the study, and quarterly at other times (or more often if needed). The UPSTREAM online detai

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results of urodynamic testing underpins the urologist's ability to make a management decision, in conjunction with his patient, so neither the man nor his urologist can be blinded to the intervention or its findings. The BRTC Quality Assurance Manager will oversee and demonstrate that BRTC's standard operating procedures for trials have been
followed and properly documented, including observance of GCP throughout. The UPSTREAM Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting. Project Management Group (PMG) The study will be supervised by a PMG. The treatment decision is between the urologist
and the patient and there are no treatment 'requirements' imposed by the UPSTREAM study. Observers may also attend, as may other members of the PMG or members of the PMC will also have an independent chair and at least two other independent
members, and will monitor accumulating trial data during the course of the trial and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or closure of the trial. If neither arm is dominant: i.e. both cheaper and more effective, then incremental cost-effectiveness
ratios will be calculated in relation to surgery rates and IPSS scores. The Trial Manager based at the BRTC will take responsibility for the day-to-day supervision of study activities. It was estimated that the equivalent of 12 recruitment months (4 centres × 3 recruitment months each) should yield 48 participants out of the overall accrual target of 800,
however, a more realistic assessment of actual recruitment time meant a revised target of 17 patients, of which we recruited 13. Invasive urodynamics is used to calculate voiding parameters (BOO index, contractility) and assess urine storage (detrusor overactivity, bladder capacity). Their guidance during the preparation of the patient consent
documentation, including information, will be vital for the success of the consent and randomisation processes. The topic guide will be devised to ensure that the primary issues are covered across all interviews, but do not dictate data collection. We have chosen 1 point on the IPSS as it is a conservative estimate of the level at which we would assume
non-inferiority, since a change of 2 points is associated with a change in global impression in urinary condition [44].Loss to follow-up in our previous trial of conservative treatment for men with urinary incontinence after prostate surgery [25] was 5 to 10 % at 1 year. As this is a pragmatic study, surgeons may feel it necessary in some cases to conduct
additional tests outside of the participant's allocated intervention group. We will also seek advice from the PP on the reporting and dissemination in Bristol (BRTC)The Study Office will be based in the BRTC within the School of Social and
Community Medicine at the University of Bristol, and will provide day-to-day support for the clinical centres. Qualitative findings will help to illuminate the perceived effectiveness and acceptability of invasive urodynamic testing for male BOO, its impact on clinical decision-making and explore any barriers to their uptake outside of the trial. Qualitative
methods have been chosen as the most appropriate means to achieving a deep understanding of beliefs and perceptions of key medical events [29, 30]. Analysis will inform further data collection: for instance, analytic insights from data gathered in earlier interviews will help identify any changes that need to be made to the topic guide during later
interviews. Thematic analysis [40], utilising a data-driven inductive approach [41], will be used to scrutinise the data in order to identify and analyse patterns and themes of particular salience for particular salience f
with the data and initial ideas noted. If it does then both the adjusted and unadjusted results will be quoted in future reports and papers. The analysis and reporting of the UPSTREAM trial will be in accordance with Consolidated Standards of Reporting Trials (CONSORT) [45] guidelines. However, outcome assessment is largely by participant self-
completed questionnaire, so avoiding interviewer bias. Methods to protect against bias Urodynamic techniques We will centrally monitor deviation will be available to participating centres, both as a telephone-based interactive voice response
(IVR) system and as an Internet-based service, for them to complete the randomisation procedure themselves, on site. Further details of 'Identification, Recruitment and Consent' are outlined below (page 10). Study outcome measures have been selected according to the specifications of the HTA commissioning brief. Primary outcome
measure • Primary clinical outcome: difference in lower urinary tract symptom (LUTS) between the 2 arms at 18 months (post randomisation), measured with the IPSS. At the baseline and 18-month follow-up clinic appointments, resource use questionnaires will be interviewer-administered if time permits, otherwise the questionnaires will be given to
the men at the clinics for them to complete in their own time, and return them by post if necessary. Data collected on the paper CRFs at study centres or as questionnaires from participants will be identifiable only by participant study number. However, entire reliance on CISC for all bladder emptying, or use of CISC to dilate a urethral stricture is not
acceptable. Planned interventions Baseline clinical guideline on Male LUTS [13]: 

Assessment of general medical history to identify possible causes of LUTS, and associated comorbidities. In addition, all deaths with any cause
(related to the trial or otherwise) should also be recorded on the 'UPSTREAM Adverse/Serious Events' form. All AEs should be reported to the UPSTREAM Study Office Team; depending on the nature of the event the reported using
the 'UPSTREAM Adverse/Serious Adverse Events' form. The cost of the interventions and the use of primary and secondary NHS services by the men, personal and social service costs, costs to the men arising from their treatment (e.g. over-the-counter medication) will be estimated through the collection of resource use data as outlined earlier and
the valuation of these data. NHS tariffs will be used to quantify the resource use information from the patients themselves. Differences in costs between the arms from each of the three perspectives will be evaluated using regression techniques adjusting
for pre-specified baseline characteristics, randomisation variables and a centre effect. All analyses will be clearly pre-defined to avoid bias. Adverse events (AE) An AE includes any untoward medical occurrence in a study participant, including abnormal laboratory results, symptoms or a disease that does not necessarily have a causal
relationship with procedures required by the protocol. The TSC will consist of a chair and at least two other independent members, and also the Trial Manager and the CI. A subset of transcripts will be discussed within the research team and
resolved in order to achieve a coding consensus and to ensure robust analysis. Data management and security - overall trialData collection and transportation All data held in Bristol will conform to the University of Bristol Data Security Policy and in Compliance with the Data Protection Act 1998. We propose using the DAMOCLES charter for
independent DMCs (IDMCs) as our reference point, which will be agreed in advance by the TSC. A two-arm trial randomising men with bothersome LUTS, for whom surgeons would consider offering surgery, between a care pathway based on urodynamic tests with invasive multichannel cystometry ('urodynamics' active intervention arm) and a care
pathway based on non-invasive routine tests: i.e. without multichannel cystometry ('non-urodynamic assessment' control arm) (see Fig. 1, study flow diagram). Fig. The CI will require a copy of the Trust Research and Development (R&D) approval letter before accepting participants into the study from that Trust (see Additional file 1 for a complete
listing of supporting Trusts). This outcome is on a continuous scale and consists of 7 questions concerning urinary symptoms with a 6- point Likert scale response from 0-5; therefore, with a minimum score of 0 and maximum score of 35. In men undergoing surgery in both arms, an additional Qmax measure at 4 months after operation will be used as
a quality measure for surgery The EuroQol Group's 5 dimension health status questionnaire (EQ-5D-5 L) will be used to provide the quality of life weights used to calculate QALYs Qualitative interviewing will explore user acceptability and influences on decisions made by the participating men and the surgeons In addition, all men will be invited to
consent to long-term follow-up, including use of computerised NHS records, Hospital Episodes Statistics (HES) data and other routine data sources. Participant entry Identification, recruitment and informed consentAll eligible men referred with voiding LUTS will be identified by the consultant, dedicated research nurse, or designated team member at
time of receipt of referral letter or during patients' clinical appointments. Once the main report has been published, a lay summary of the findings will be sent in a final UPSTREAM newsletter to all involved in the trial. The PMG will meet monthly for the first 6 months from study start and quarterly thereafter. Purposive sampling will ensure that
adequate numbers of interviews will be conducted with men from each of the possible randomised groups according to treatment allocation. The data will be explored by comparison with the whole dataset. Transcripts from the patients' and health care professionals' interviews will be
analysed separately, with coding frames being developed for each separate phase of the research. The components and timing of follow-up measures are shown in Table 1. Table 1 Measurement outcomes table: components/timing Where possible, telephone interviews will be conducted with men who withdrew or declined randomisation. Steps will be
taken to minimise loss to follow-up, including reminder letters and telephone calls. Staff will be asked in the 18-month CRF to record whether or not they knew which group the man had been allocated to, and hence which diagnostic tests were performed before undertaking outcome assessments. All NHS IT systems will be similarly supported. The
baseline RUL (0-6 months) will be given to the patients at the baseline assessment clinic; all subsequent RULs will be posted by the UPSTREAM Office Team. Randomisation will utilise the existing proven remote automated computer randomisation will provide
clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data). As a pragmatic trial, standard practice for the centres will be followed, relating to type of surgery (providing it is a NICE-approved surgical procedure, e.g. monopolar or bipolar TURP, or laser), whether to stay on
LUTS medications, antibiotic prophylaxis and other factors. All analyses will be on an intention-to-treat (ITT) basis where men are assessed in the groups to which they were assigned at randomisation. All men will be actively followed up, with analysis based on the intention-to-treat principle. This is because the likely reduction in surgery rates in the
former group due to more accurate diagnosis should not disadvantage them in terms of clinical improvement. The researcher will use open-ended questioning techniques to elicit participants' own experiences and views of key events and participants will be carried out on the primary
analysis (IPSS score) and main secondary outcome (surgery rate). These will be reviewed by the UPSTREAM Office Team (BRTC) on a monthly basis. Due to variation in patient pathways in each hospital, these arrangements should be individualised according to local circumstances in each site. For men who are randomised, the research centre should be individualised according to local circumstances in each site.
also record that the patient opted for this consent and randomisation approach in their medical notes, and in the UPSTREAM Baseline CRF (Comments section). Study specific procedures for a participant's change of permissions, or withdrawal, are outlined in the relevant trial working guidelines. Randomisation, blinding and prevention of
bias Randomisation All men who enter the trial will be logged with the central study office and given a unique, six-digit study (participant) identification number. Symptomatic outcome of surgery is confounded by a number of factors for which we cannot control. For example, the following tests may be undertaken in line with the NICE clinical guideline
on Male LUTS [13]: Information, advice and time to decide if they wish to have prostate specific antigen (PSA) testing if their LUTS are suggestive of BPO, or their prostate feels abnormal on DRE, or they are concerned about prostate specific antigen (PSA) testing if their LUTS are suggestive of BPO, or their prostate feels abnormal on DRE, or they are concerned about prostate specific antigen (PSA) testing if their LUTS are suggestive of BPO, or their prostate feels abnormal on DRE, or they are concerned about prostate feels abnormal on DRE, or they are suggestive of BPO, or their prostate feels abnormal on DRE, or they are suggestive of BPO, or their prostate feels abnormal on DRE, or they are suggestive of BPO, or their prostate feels abnormal on DRE, or they are suggestive of BPO, or their prostate feels abnormal on DRE, or they are suggestive of BPO, or their prostate feels abnormal on DRE, or they are suggestive of BPO, or their prostate feels abnormal on DRE, or they are suggestive of BPO, or their prostate feels abnormal on DRE, or they are suggestive of BPO, or their prostate feels abnormal on DRE, or their prostate f
symptoms, or pain Imaging of the upper urinary tract when clinically indicated: e.g., chronic retention, haematuria, recurrent infection, sterile pyuria, or pain Interventions for randomised men'Non-urodynamic assessment' control arm (usual care)Men will have clinical treatment based on the baseline clinical assessment described
above. Intervention arm (usual care plus urodynamics assessment) Men will undergo the routine baseline clinical assessments set out above. The CRFs will be used to measure: the initial hospital resource use during the diagnostic phase of the trial; the perioperative stay for those men who subsequently undergo surgery and, with the exception of this
surgery, any in-patient stays, out-patient stays, out-patient visits and procedures occurring at the treating hospitals, where the study has research governance approval, from the end of the diagnostic phase until the end of the 18-month clinic follow-up. The
difference between the scores for the two pathways will be evaluated using linear regression, adjusting for centre and IPSS score at baseline. Health care professionals will also be interviewed at the end of the trial to gather data on their views and experiences of assessment with and without urodynamics, information and support needs and their
attitudes to its future implementation. Health care professionals (e.g. urologists, urodynamics technicians, nurses, etc.) involved in the trial will be determined by the need to achieve data saturation, such that no new themes are
emerging from the data by the end of data collection [39]. Using the more conservative difference we expect the intervention arm. Symptom scores will potentially improve for those men in both arms who undergo appropriate surgery. A copy of the completed form
should be kept in the Site File and in the patient's notes. Serious adverse events (SAEs) Local PI or Research Nurse: all SAEs including deaths from any cause (related or otherwise) should be recorded on the 'UPSTREAM Adverse/Serious Adverse Events' form, whether originally notified on a CRF, participant questionnaires or by other means. A
sensitivity analysis will also be conducted to assess the treatment effect for those who fully comply with the intervention. Analysis of secondary outcomes listed in the 'outcomes' section will be analysed using appropriate regression models, adjusting for centre and the baseline measure of the outcomes' section will be analysed using appropriate regression models, adjusting for centre and the baseline measure of the outcomes' section will be analysed using appropriate regression models, adjusting for centre and the baseline measure of the outcomes' section will be analysed using appropriate regression models, adjusting for centre and the baseline measure of the outcomes' section will be analysed using appropriate regression models, adjusting for centre and the baseline measure of the outcomes' section will be analysed using appropriate regression models, adjusting for centre and the baseline measure of the outcomes' section will be analysed using appropriate regression models.
BRTC Randomisation system infrastructure is also maintained by University Information Services. Auditing and inspection The study may be subject to inspection and audit by North Bristol NHS Research Governance Framework for Health
and Social Care (2nd edition). Statistics and data analysisSample size determinationWe decided that the important consideration is that the group of men randomised to having urodynamics should have clinical outcomes which are not inferior (rather than equivalent) to those who are randomised to management without urodynamics. They will also
help ensure appropriate approaches to the delivery of the diagnostic/treatment pathway, especially the approach to the doctor/patient decision system provided by the BRTC. (Note: a urinary flow rate test, recorded up to 6 months prior
to date of informed consent, is acceptable to avoid unnecessary repeat for the patient) Discretionary testsAs this is a pragmatic trial, additional tests may be undertaken according to the usual practice of the research sites. Delegated responsibilities will be assigned to the NHS trusts taking part in this trial. FundingThe National Institute for Health
and Research, HTA programme are funding this study (project number 12/140/01). Publication policyThe main forms of dissemination will be through the academic press, HTA monograph, guidelines and workshops for clinical staff and by lay summaries on websites and other more accessible forms for patients. Those patients identified from referral
letters will be sent a Patient Information Sheet (PIS), Assessment Information Sheet (PIS), Assessment Information Sheet (PIS), and covering letter. This will facilitate the use of regression modelling to adjust for pre-specified baseline characteristics, randomisation variables and centre effects. Uncertainty for all these analyses will be addressed using cost-effectiveness acceptability curves
and sensitivity analyses. After at least 24 hours, the centre should contact the patient by telephone to confirm whether they are still willing to proceed with the study, and if so, the centre can proceed with randomisation and inform the patient of his intervention allocation via the telephone. Hence, it should distinguish men with BOO, who should
benefit from surgery to relieve obstruction, from men with reduced bladder contractility, who are unlikely to benefit from surgery, or those without obstruction with storage disorders or normal urodynamic findings. Method of urodynamic testing Quality of urodynamic testing will be according to International Continence Society Good Urodynamic
Practice requirements [22]. The chair of this group will be the CI and will consist of grant holders, representative from the PP. The PIS and the consent form will refer to the possibility of long-term follow-up and being contacted about other research if the man is willing. However, any hospitalisation of a
pre-existing condition resulting from worsening, or elective procedures booked after the patient has signed the consent form would constitute an AE. Serious adverse event (SAE) if it: results in death of the participant is life-threatening; the term 'life-threatening' refers to an event in which the
participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe requires hospitalisation, or prolongation of existing inpatient hospitalisation, or prolongation of existing inpatient hospitalisation.
investigator* *Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definitions above, may also be considered serious. All men who enter the study will be logged with the central trial office and
given a unique six-digit study (participant) identification number, and randomised. We do not feel it is necessary or ethical to perform sham catheterisation to conceal the nature of testing. Type of surgery will be recorded. They will be recorded. They will be recorded. They will be recorded first
to study collaborators. In such a way that the resource use collected can be costed using NHS tariffs. Qualitative data collection The aim of the study is to understand patients' and health care professionals' views and experiences of invasive urodynamic testing for male BOO and BOO surgery. Objectives: To explore through qualitative methods
patients' views, experiences and beliefs about LUTS To examine patients' understanding and knowledge of testing for BOO and treatment expectations. acceptability and feasibility and feasibility of invasive urodynamic testing/non-urodynamic
assessment To investigate patients' and health care professionals' decision-making regarding surgery for male BOO To use qualitative methods to understand barriers and health care professionals in relation to invasive urodynamic testing
and BOO surgery To investigate patients' and health care professionals' experiences of invasive urodynamic testing for male BOO we will conduct in-depth semi-structured qualitative interviews with patients and health care
professionals involved in their care. At baseline, 6 and 12 months follow-up the men will be given a study designed Resource Use Log (RUL) to be used as an aide memoire in which to record prospectively NHS hospital and community-based health care use, medications, social service resource use, time off work and any other expenses resulting from
their treatment. An independent Data Monitoring Committee will review confidential interim analyses of accumulating data at its discretion. Economic evaluation The trial will include a formal economic evaluation comparing the costs and cost-effectiveness of the interventions from the perspectives of the NHS, personal social services and patients. The
main secondary outcome for this trial is the uptake of surgery in each pathway; this will be analysed using logistic regression. Personal data (e.g. name and address, or any data from which a participant. Access to the dataThe Senior IT Manager (in collaboration
with the CI) will manage access rights to the data set. This is likely to include up to 30 health care professional and 45 face-to-face trial participation or withdrew from the trial. The sampling frame is shown in Table 2. Table 2 Sampling frame A flexible topic guide will be used
in order to assist questioning during in-depth individual interviews. All participants will be offered a lay summary of the main findings of the study must be submitted for Site Specific Assessment (SSA) at each participants will be offered a lay summary of the main findings of the study. The study must be submitted for Site Specific Assessment (SSA) at each participants will be offered a lay summary of the main findings of the study.
the study administrative centre in the Bristol Randomised Trial Centre (BRTC, a fully registered UK CRN clinical trials unit) in the University of Bristol. Detailed reporting procedures for SAEs are found in trial specific working guidelines. Chief Investigator (CI)/or Trial Manager: The Trial Manager will inform the CI of all SAEs. If, in the opinion of
the local PI and the CI, the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event is confirmed as being serious and related and unexpected, the CI or Trial Manager will not be a serious and related and unexpected and unexpected and unexpected as the confirmed as a serious and related and unexpected and unexpec
Other symptom scores such as the ICIQ-MLUTS, which is potentially more sensitive but less widely recognised, will be evaluated in a similar way to the IPSS primary outcome; adjusting for centre and baseline scores. Interviews allow for the exploration of complex and sensitive issues, allowing participants to engage in a dialogue in their own
language and drawing on their life experiences to explore the issues which are important to them. Previous studies have successfully utilised qualitative methods to investigate patients' views, experiences and health beliefs about LUTS [31-34], triggers and barriers to help seeking [35] perspectives on treatment outcomes [36]. The CRFs will be
designed so that the resource use collected can be costed using NHS tariffs. All other data collected for such a patient, however, such as baseline questionnaires, should be suitably discarded by the research site; the trial has no need to retain this information as the patient has decided not to enrol (be randomised) into the trial. For this reason, chief
credit for the study will be given, not to the committees or central organisers, but to all those who have collaborated in the study. The PP of service users and thresholds of testing were informed by a preliminary survey of 30 UK surgeons in 22
departments, which we undertook in 2012. Any differences in excess of 0.5 SDs or 10 % or more will be controlled for in sensitivity analyses to ensure that the imbalance does not affect the overall result. The topic guide will incorporate considerable flexibility to enable participants to introduce new issues unanticipated by the researchers. If the
patient agrees to the study, they will be given a chance to ask questions and should ideally have at least 24 hours to think about taking part before being consented and randomised. For clarity, a copy of the consent form and completed Change of Permissions/Withdrawal Form should be kept at site, as well as forwarded to the UPSTREAM Office Team
for records. All outcomes will be described and compared with the appropriate descriptive statistics where relevant: mean and SD for continuous and numbers and percentages for dichotomous and categorical outcomes (e.g., subjective recurrence of
incontinence). Analysis of the primary outcome The primary outcome will be the IPSS score at 18 months post randomisation. Firstly, participants will be interviewed 1 week after a decision has been made regarding treatment. Delays in centres being ready for the trial and additional work to improve recruitment amongst centres that were ready
meant this initial verification window was too narrow. The main analysis will be performed when all 18-month follow-ups have been completed. Other non-voting members will include the grant holders. Alternatively, the research nurse will describe the study to the patients at their clinical appointment and, if interest is expressed, provide further
details of the study by means of the PIS and AIS. We will take very active measures to minimise loss of men from the study in line with Research Ethics Committee approval, such as reminder letters, phoning/texting/ emailing the men, obtaining back-up 'best contact' addresses, using non-contingent retention incentives [26], and checks with their GPs
[27]. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses. IT security and maintained by the University of Bristol Information Services will have infrastructure including server and server-based applications and desktop system maintenance. Free flowers to enable international prospective meta-analyses.
rate testing (maximum flow rate, voided volume (VV), post-void residual) will be used at baseline and 18 months; an additional measurement of flow rate in men undergoing surgery in both groups at 4 months after surgery (± 1 month) will provide objective assessment of effective relief of BOO. The main report will be drafted by the PMG and
circulated to all clinical collaborators for comment. Subgroup analyses will, therefore, be carried out to assess the difference in treatment effect for pre-specified analysis plan will be created in which the plausible assumptions about missing data will be created. Subsequent need for surgery (related to
their LUTS) during any stage of the trial will be recorded Adverse events of testing and treatment (e.g. infection, urinary retention). Measures from the International Consultation on Incontinence Questionnaires (ICIQ) [24] will be used alongside the IPSS, giving sensitive and comprehensive assessment of LUTS severity/bother, sexual function,
quality of life and satisfaction with urodynamic testing. To assess non-inferiority of IPSS the post-treatment difference at 18 months between the 2 arms will be examined and a mixed model approach with treatment group as a fixed factor and investigational site as a random
effect will be considered. The primary analysis will be based on the observed data supported by a sensitivity analysis where all missing data will be imputed at baseline CRF, whether the participant received the diagnostic assessments that
they were randomly allocated to, and provide reason(s) if assessment was different to that allocated. Hospital staff will be informed about the study by the Principal Investigator (PI) and
the research nurse, so that they can answer queries from participants and their relatives. Withdraw or if they are unable to continue for a clinical reason. Information capable of identifying individuals and the nature of treatment received will be held in the database with
passwords restricted to UPSTREAM study staff. Audio recordings of qualitative data made during the interviews will only refer to the participant by their study number. Retention of dataPatient identification codes will be held by BRTC for 15 years after the close of the study. The process of constants
comparison will allow for the generation of new themes, re-classify themes and incorporating themes within other themes [42, 43] and the coding frame will be modified, if needed, as analysis develops. They will review communications in respect of clarity and avoidance of potential ambiguity. However, to our knowledge to date no studies have
examined patients' and health care professionals' views and experiences regarding invasive urodynamic testing for BOO. As we are recording assessment allocation in trial document, such a deviation would not require additional 'Protocol Noncompliance' reporting. All other Good Clinical Practice (GCP) and/or protocol
deviations should be recorded on the 'GCP/Protocol Noncompliance Report Form' (provided in the Site File) and forwarded to the Trial Manager who will notify the Chief Investigator (CI) and Trial Sponsor. Allocation to trial groups and willing men will be randomly allocated to receive one of two assessment pathways, as outlined above; that
is either a) usual care (non-urodynamics, control); or b) usual care plus urodynamics assessment (intervention). All men who enter the study (participant) identification number. We aim to capture urologist and patient opinions about treatment decisions in the relevant case
report form(s) (CRF). In all instances it will be up to the physicians responsible for the participants' care to determine whether the person's change in health is related to the trial. AEs are not: continuous and persistent disease being studied; or continuous and persistent disease or symptom, present before the trial and the physicians responsible for the physicians 
treatment failure For the UPSTREAM study, pre-planned hospitalisation or elective procedures: e.g. for pre-existing conditions which have not worsened, does not constitute an AE. Missing items on the health-related outcome measures will be treated as per the instructions for that particular measure and imputed if necessary. The completed form
should then be forwarded to the Trial Manager within 24 hours of learning of a SAE, or within 24 hours in the event of death. Participants are informed in the PIS that they have the right to withdraw all personal data held by the study. Review of current medication Physical examination guided by urological symptoms and other medical conditions,
an examination of the abdomen and external genitalia, and a digital rectal examination (DRE) Urinary frequency volume chart (bladder diary) Virinary frequency volume chart (bladder diary) Measurement of urinary flow rate, with post-void residual volume measurement by ultrasound. These currently include: Southmead Hospital, Bristol
Freeman Hospital, Newcastle upon Tyne; Royal Devon and Exeter; Musgrove Park Hospital, Epsom; Oueen Elizabeth Hospital, Birmingham; Kent and Formby District General Hospital, Epsom; Oueen Elizabeth Hospital, Birmingham; Kent and Formby District General Hospital, Epsom; Oueen Elizabeth Hospital, Birmingham; Kent and Formby District General Hospital, Epsom; Oueen Elizabeth Hospital, Birmingham; Kent and Formby District General Hospital, Epsom; Oueen Elizabeth Hospital, Birmingham; Kent and Formby District General Hospital, Epsom; Oueen Elizabeth Hospital, Birmingham; Kent and Formby District General Hospital, Epsom; Oueen Elizabeth Hospital, Birmingham; Kent and Epsom; Oueen Elizabeth Hospital, Epsom; Oueen Elizabeth H
Canterbury Hospital, East Kent and Canterbury; Salisbury; Lister Hospital, Middlesbrough; The Queen Elizabeth Hospital, Stevenage; Churchill Hospital, East Kent and Canterbury; Salisbury; Lister Hospital, Stevenage; Churchill Hospital, Stevenage; Churchill Hospital, Middlesbrough; The Queen Elizabeth Hospital, Stevenage; Churchill Hospital
Torbay; Southampton General Hospital, Southampton; Kettering General Hospital, Reading; Derriford Hospital, London; Royal Berkshire Hospital, London; Royal Berkshire Hospital, Plymouth; West Cumberland Hospital, London; Royal Berkshire Hospital, London; Royal Berkshire Hospital, Southampton; Kettering; Charing Cross Hospital, London; Royal Berkshire Hospital, London; Royal Berk
required. Participants Men with bothersome LUTS and suspected BOO for whom surgeons would potentially offer surgery. Inclusion criteria • Unable to pass urine without a catheter (urinary retention) (excluding clean intermittent self-
catheterisation (CISC) after void to empty)* Relevant neurological disease, such as a stroke, multiple sclerosis, Parkinson's disease, or spina bifida (diabetes mellitus is not an exclusion criterion unless it is causing diabetic neuropathy) Undergoing active treatment, or on active surveillance, for prostate or bladder cancer (including low-grade/stage
transitional cell cancer) revious prostate surgery Not medically fit for surgery, or unable to complete outcome assessments Men who do not consent to be randomised and/or are not willing or able to complete outcome assessments Men who do not consent to be randomised and/or are not willing or able to complete outcome assessments Men who do not consent to be randomised and/or are not willing or able to complete outcome assessments and one consent to be randomised and/or are not willing or able to complete outcome assessments and one consent to be randomised and/or are not willing or able to complete outcome assessments and one consent to be randomised and/or are not willing or able to complete outcome assessments and one consent to be randomised and/or are not willing or able to complete outcome assessments.
assuming no difference between the groups, a trial of 310 men per arm will give 80 % power to rule out a non-inferiority margin of 1 point below the mean IPSS in the non-urodynamic arm, using a 1-sided t test (common standard deviation [SD] of 5) at the 5 % significance level. The final version will be agreed by the Steering Committee before
submission to the funders (National Institute for Health Research (NIHR) HTA) and subsequent publication in a peer-reviewed journal, on behalf of all the UPSTREAM collaborators. To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior agreement from the PMG. We
intend to maintain interest in the study by publication of UPSTREAM newsletters at intervals for participants, staff and collaborators. We are combining qualitative methods and controlled trial methods as has long been advocated [37]. Study designIn-depth interviews [38] will be conducted with trial participants (from all arms of the trial). All
investigators are already experienced urodynamics investigators, or work with an experienced urodynamics unit meeting the national minimum standards. Standardisation of surgical techniques are already experienced urodynamics investigators are already experienced urodynamics investigators.
questionnaires, there and then, but does not randomise the patient until at least 24 hours have passed. Dissemination to clinicians will be through papers in major urology journals and conferences (e.g. the European Association of Urology), workshops and presentations to national meetings: e.g. the British Association of Urological Surgeons (BAUS),
which is the specialist body with the responsibility for guiding clinical practice, policy matters, research priorities, governance and training in matters related to male LUTS. Sub-studies will also be conducted on the trial results, written up and submitted for publication in peer-reviewed journals. The success of the study depends entirely on the
wholehearted collaboration of a large number of men undergoing investigation for BPO surgery, as well as their nurses and doctors. Interviews will be checked for accuracy and then imported into NVivo qualitative data analysis software (QSF)
International, Daresbury, UK) which aids the management and indexing of qualitative data. These interviews will consider and experiences of the trial, explore participants' e
and information and support needs. A second interview will be conducted with a second group of participants 18 months after randomisation (after treatment and recovery. Telephone interviews will be conducted with a sample of men who withdrew from the trial. If the
patient is happy to take part in the study without having been given PIS and study details over the previous 24 hours, and requests to provide written consent and complete baseline questionnaires at that time (i.e. to avoid having to return to the hospital for an additional appointment) this is possible. These logs will reflect the design of the 6, 12 and
18-month resource use questionnaires respectively. At 6-month and 12-month follow-up, self-completed resource use questionnaires will be included within the questionnaires given to all men at baseline, 6, 12 and 18 months follow-up. Medical record
abstractionAt 18 months follow-up, in-patient stays, out-patient visits and procedures relating to the man's urinary symptoms, identified though the 18-month resource use questionnaire occurring in the treating hospitals, where the study has research governance approval, will be abstracted from the patients' medical records. We therefore calculated
our sample size based on both the primary outcome and surgery rates: non-inferiority of symptoms at 18 months after randomisation; and a reduction in surgery rates in the intervention arm. In Bristol, audit data for 5670 men presenting with LUTS suggestive of poor or obstructed urine flow show that 73 % to 83 % would have surgery. One aspect of
uncertainty is likely to be that of missing data. The following technical aspects of invasive urodynamic testing will be reviewed for each centre (mandatory): Appropriate equipment maintenance and calibration testing consistent with manufacturer instructions according to the unit log Measurement of bladder and abdominal pressure, including
resting pressures within expected limits Concurrent computing of detrusor pressure Extrinsic filling at 'physiological rates' Checks of pressure transmission (e.g. subtraction of cough impulse) during filling and after voiding Trace labeling for later re-interpretation; e.g. reporting of key events (e.g. detrusor overactivity, permission to void),
bladder sensations and timing of 'provocation tests' and 'permission to void' Correction for artefacts during computation of BOO and bladder contractility indices.
urodynamics, patients will see their surgeon to decide on whether to proceed to surgical treatment. In particular, the primary outcome measure (IPSS at 18-months post randomisation) could be collected via the telephone if necessary. Economic data collection relation to the management of bothersome LUTS will be measured from
randomisation to 18-month follow-up. The same model specification will be used to evaluate the differences in QALYs. For each of the three perspectives the difference in costs and in effectiveness in terms of surgery rates and IPSS scores will be examined. In addition, they will undergo invasive urodynamics, in which catheters are used to measure
bladder and abdominal pressures, during bladder filling and passing urine. Formal tests of interaction between the different subgroups of patients. Of note, subgroup analysis will be carried out for men presenting with more and less
substantial storage LUTS (urgency, increased frequency and nocturia), based on the IPSS storage subscore and/or the ICIQ MLUTS storage score. Subgroup analysis will be undertaken for the differing clinical diagnoses reached at the 'Clinical Decision' stage; all of the factors below are on a Yes/No basis: Voiding dysfunction due to BOO, with or
without reduced bladder contractility Voiding dysfunction due to reduced bladder contractility, with or without BOO Storage dysfunction (nocturia) Proposed frequency of analysesMen will be followed up at 6 months (by post), 12 months (post), and 18 months (clinic), after
randomisation. Acute urinary retention as a possible complication will also be examined as secondary outcome. Planned further analyses in batches, and sampling will continue until no new themes are emerging from the
interviews. An approved study-specific poster can also be displayed in suitable clinic rooms, which provides the contact for further information. If a participant withdraws consent, further participant questionnaires will not be collected. In addition, we will obtain consent from the men to
enable us to access centrally-held NHS data; e.g., via the NHS Strategic Tracing Service in England and Wales to find new addresses, and electronic data linkage which records any in-patient episodes and outpatient visits. Other sources of bias (detection bias) Where feasible, research staff will be blinded to allocation while conducting data collection
for outcomes, performing data entry and analysis, and by using study numbers only to identify men, questionnaires and diaries. The sponsor will provide an assessment of the SAE 

The CI (or Trial Manager) will report any related and unexpected SAEs to the main Research Ethics Committee and the Data Monitoring Committee (DMC) within 15 days
of the CI becoming aware of it All related SAEs will be summarised and reported to the Ethics Committee, the Funder, the DMC and the Trial Steering Committee (TSC) in their regular progress reports Assessment and follow-upClinical outcomes Will be assessed by participant-completed questionnaires at baseline, 6 months
(postal (or online or by telephone if required)), 12 months (postal (or online or by telephone interviews will be conducted with those who declined to be randomisation (clinic appointment). In addition, telephone interviews will be sought for the research team to continue to collect
outcome data from their health care records. For all analyses carried out, effects estimates will be presented along with confidence intervals and p values. Men who are not willing to be randomised, but who would otherwise be eligible, will be asked to consent to being contacted for qualitative research to explore reasons for non-participation. This
alternative consent and randomisation process helps the patient to avoid returning the hospital simply for the purpose of the trial. Medical judgment will be exercised in deciding whether an AE is serious in other situations. Expected, related adverse events Within UPSTREAM, an AE is defined as 'related' if it occurs as a result of a procedure required
by the protocol, whether or not this procedure is the specific intervention under investigation and whether or not it would have been administered outside the study as normal care. The following events are expected, related AEs during/after any diagnostic procedures: 

urinary tract infection 

have been administered outside the study as normal care. The following events are expected, related AEs during/after any diagnostic procedures:
discomfort discomfort dysuria discomfort dysuria discomfort discom
embolism prolongation of post-operative catheterisation cathet
classification in trial CRFs [28]. Reporting procedures for adverse events Within UPSTREAM, all adverse (serious and non-serious) events should be recorded on the 'UPSTREAM Adverse Events' form, whether originally notified on a CRF, participant questionnaires or by other means. The CI, all PIs, study coordinators, research
nurses, and BRTC personnel will have undertaken the mandatory GCP training. Regulatory issues Ethics approval from the 4 centres recruited 58 participants, exceeding the agreed target by 16. Strategic findings from the
second feasibility phase, and implications for the trial overall, are outlined in the discussion section of this paper (PPI)An expert panel (PPI)An expert p
the study. All conservative and surgical management plans and actual treatment received will be documented. Written informed consent will be obtained from all patients who agree to take part in the study, while the Senior Trials Manager will
provide mentoring and guidance to the Trial Manager and advice to the team on generic coordination issues. Hospital staff should complete trial-specific screening logs for all potentially eligible men and provide confirmation of the patient was eligible but
declined to take part; and 3) patient was eligible and consented to take part. The initial cumulative accrual prediction was based on a relatively simple linear trend assumption without incorporating differential recruitment rates within centres. Data is stored centrally on robust data systems with file
versioning and recovery and mirroring on a second site. The following will be measured at 6, 12 and 18 months: ICIQ wodynamics satisfaction (ICIQ-MLUTS) ICIQ wodynamics wodynamics satisfaction (ICIQ-MLUTS) ICIQ wodynamics wodynamic
• Qmax at 18 months. Men will be asked not to reveal information about their diagnostic evaluation and treatment. However, a more conservative estimate of just over 20 % loss to follow-up has been used in the sample size calculations. As this is a pragmatic trial, surgical procedure and post-operative care will be according to local centre
practice.Loss to follow-up (attrition bias)Loss to follow-up in our previous trial of conservative treatment for men with urinary incontinence after prostate surgery [25] was 5 to 10 % at 1 year. Topic guides will be modified as necessary throughout the course of the study to reflect findings as they emerge. The differences in costs and QALYs will be
examined using the net benefit framework over a range of values for the QALY. This showed that the minimum baseline dataset comprises IPSS, Qmax with post-void bladder ultrasound scan and urinalysis. Setting Urology departments of at least 26 NHS Hospitals in the UK. The research nurses and the surgeons will complete a Peri-Operative CRF at
the time of surgery, including any intra-operative difficulties or complications. Therefore, sample size will be 388 per arm to take into account 20 % loss to follow-up. These assumptions will then be tested within the sensitivity analyses. Internal feasibility phase and recruitment ratesAn internal feasibility phase, intended to verify that recruitment is
possible, was first conducted in 4 centres between months 7 and 9 (October-December 2014). It is anticipated that both the TSC and the DMC would meet twice a year, once face-to-face and once via teleconferencing. If an invasive urodynamics test was conducted on the same men, the data indicate that surgery would only be carried out in 60 %,
based on the prevalence of impaired bladder contractility 
assigned to the segments of the data that provide insight into the participants' views and understanding of their experiences
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