BMJ Open

A study protocol for a randomised feasibility study COmparing Urolift and Standard Transurethral resection of prostate Ahead of Radiotherapy in men with urinary symptoms secondary to prostate enlargement in Southwest London and North Cumbria (COSTAR).

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-076621.R2
Article Type:	Protocol
Date Submitted by the Author:	08-Aug-2023
Complete List of Authors:	Wong, Kathie; Royal Marsden NHS Foundation Trust, Urology; North Cumbria Integrated Care NHS Foundation Trust, Urology Kinsella, Netty; The Royal Marsden NHS Foundation Trust, Urology Seth, Jai; St George's Hospital, Urology Nicol, David; The Royal Marsden NHS Foundation Trust, Urology Cahill, Declan; The Royal Marsden NHS Foundation Trust, Urology Kasivisvanathan, Ramanathan; Royal Marsden NHS Foundation Trust, Department of Surgery and Anaesthesia Withington, John; University College London Moghul, Masood; Royal Marsden Hospital NHS Trust Moss, Charlotte; King's College London, Translational Oncology and Urology Research Van Hemelrijck, Mieke; Kings College London, Translational Oncology & Urology Offices Giorgakoudi, Kyriaki; City, University of London; NIHR biomedical research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research UK Cottrell, Chris; The Royal Marsden NHS Foundation Trust, Urology Yates, Emma; Royal Marsden Hospital NHS Trust Khoo, Vincent; Royal Marsden NHS Foundation Trust, Department of Oncology; Institute of Cancer Research Division of Cancer Therapeutics James, Nicholas; The Royal Marsden NHS Foundation Trust; Institute of Cancer Research Division of Cancer Therapeutics
Primary Subject Heading:	Urology
Secondary Subject Heading:	Oncology, Qualitative research, Radiology and imaging, Patient-centred medicine, Health economics
Keywords:	ONCOLOGY, Urological tumours < ONCOLOGY, Prostate disease < UROLOGY, Urological tumours < UROLOGY, RADIOTHERAPY, Magnetic resonance imaging < RADIOTHERAPY

A study protocol for a randomised feasibility study **CO**mparing Urolift and **S**tandard **T**ransurethral resection of prostate **A**head of **R**adiotherapy in men with urinary symptoms secondary to prostate enlargement in Southwest London and North Cumbria

COSTAR

Kathie Wong, Netty Kinsella, Jai Seth, David Nicol, Declan Cahill, Ramanathan Kasivisvanathan, John Withington, Masood Moghul, Charlotte L Moss, Mieke Van Hemelrijck, Kyriaki Giorgakoudi, Chris Cottrell, Emma Yates, Vincent Khoo, Nicholas James

Chief Investigator (Corresponding author):	Kathie Wong Consultant Urological Surgeon The Royal Marsden Hospital Fulham Road London SW3 6JJ Kathie.wong2@nhs.net Tel: +44 20 7352 8171
Principal Investigators:	Professor Nicholas James Professor of Prostate and Bladder Cancer Research The Royal Marsden Hospital / Institute of Cancer Research UK Nick.james@icr.ac.uk Mr Jai Seth Consultant Urological Surgeon St Georges University Hospital J.seth@nhs.net Miss Kathie Wong

	Consultant Urological Surgeon North Cumbria Integrated Care Trust
Co-investigators:	Dr Netty Kinsella (PPI lead) Nurse Consultant The Royal Marsden Hospital Netty.kinsella@rmh.nhs.uk Professor David Nicol Chief of Surgery /Consultant Urological Surgeon The Royal Marsden Hospital David.nicol@rmh.nhs.uk Mr Declan Cahill Clinical Lead / Consultant Urological Surgeon The Royal Marsden Hospital Declan.Cahill@rmh.nhs.uk Dr Vincent Khoo Consultant Oncologist The Royal Marsden Hospital / Institute of Cancer Research UK Vincent.Khoo@rmh.nhs.uk Dr Ramanathan Kasivisvanathan Consultant Anaesthetist The Royal Marsden Hospital

	Ramanathan.Kasivisvanathan@rmh.nhs.uk Mr John Withington Consultant Urological Surgeon University College London Gower Street London WC1E 6BT J.withington@ucl.ac.uk Mr Masood Moghul Clinical Research Fellow Royal Marsden Hospital Masood.Moghul@rmh.nhs.uk
Statisticians:	Professor Mieke Van Hemelrijck Professor in Cancer Epidemiology Kings College London Strand London WC2R 2LS Mieke.vanhemelrijck@kcl.ac.uk Charlotte L Moss Database and Project Manager Charlotte.moss@kcl.ac.uk
Health Economist:	Dr Kyriaki Giorgakoudi Senior Health Economist City, University of London Northampton Square, London EC1V 0HB

	NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, UK K.Giorgakoudi@city.ac.uk
Patient Representative:	Chris Cottrell Chris@theexerciseclinic.co.uk
Trial Manager	Emma Yates Clinical Research Operations Manager The Royal Marsden Hospital CO-STAR@rmh.nhs.uk

Sponsor: The Royal Marsden NHS Foundation Trust

Address: The Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ

Site Address:

The Royal Marsden NHS Foundation Trust, Fulham Road, London, SW3 6JJ

The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT

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

North Cumbria Integrated Care Trust, Newtown Road, Carlisle CA2 7HY

Role of Sponsor:

The Sponsor has responsibility for the legal aspects of the trial, helping to support delivery and provide independent review of the safety and clinical aspects of the trial. The Sponsor is responsible for hosting the trial database.

Funded by the National Institute of Health Research, Research for Patient Benefit grant (NIHR 203152)

Abstract

Introduction

Patients undergoing prostate radiotherapy with an enlarged prostate can have short and long term urinary complications. Currently, Transurethral resection of the prostate (TURP) is the mainstay surgical intervention for men with urinary symptoms due to an enlarged prostate prior to radiotherapy. UroLift (NeoTract Inc., Pleasanton, CA USA) is a recent minimally invasive alternative, widely used in benign disease but is untested in men with prostate cancer.

Methods and Analysis

A multi-centre, two-arm study designed in collaboration with a Patient Reference Group to assess the feasibility of randomising men with prostate cancer and co-existing urinary symptoms due to prostate enlargement to TURP or UroLift ahead of radiotherapy.

45 patients will be enrolled and randomised (1:1) using a computer-generated programme to TURP or UroLift.

Recruitment and retention will be assessed over a 12-month period. Information on clinical outcomes, Adverse Events, and costs will be collected. Clinical outcomes and Patient Reported Outcome Measures (PROMs) will be measured at baseline, six-weeks post-intervention and three months following radiotherapy. A further 12 in-depth interviews will be conducted with a subset of patients to assess acceptability using the Theoretical Framework of Acceptability.

Descriptive analysis on all outcomes will be performed using Stata (StataCorp 2021).

Ethics and Dissemination

The trial has been approved by the Research Ethics Committee (REC) NHS Health Research Authority (HRA) and Health and Care Research Wales (HCRW). The results will be published in peer-reviewed journals, presented at national meetings and disseminated to patients via social media, charity and hospital websites.

Trial registration IRAS 280225 Clinicaltrials.gov NCT05840549

Keywords

Urolift, transurethral resection of prostate, prostate radiotherapy, prostate cancer, urinary symptoms, bladder outlet obstruction

Strengths and Limitations

- This study is designed in partnership with patients
- Randomisation of patients to the two treatment arms avoids selection bias

- A mixed methods approach allows for maximisation of data collection
- As this is an open label interventional study, it is not possible to blind patients or surgeons to the treatment assigned to patients therefore potentially introducing bias
- This study is a pilot study aimed at assessing feasibility of randomisation and is therefore not powered to detect differences in treatment outcomes

Background

Approximately 14,000 men undergo radical radiotherapy for prostate cancer in England every year, over 85% of men are over 60 years of age and half will have lower urinary tract symptoms (LUTS) secondary to prostatic enlargement(1, 2).

The short-term complications of untreated bladder outlet obstruction from prostatic enlargement in the context of prostate radiotherapy, although rare, can be disastrous, resulting in urinary retention, sepsis and renal failure. In the long-term, urinary symptoms can continue to worsen compounded by the effects of radiotherapy. Transurethral Resection of Prostate (TURP) is the mainstay surgical intervention for outlet obstruction due to prostate enlargement prior to radiotherapy. Studies reporting functional outcomes in patients undergoing TURP and radiotherapy are limited(3, 4). TURP and radiotherapy can both cause incontinence independently and the available evidence suggests a risk of incontinence as high as 27% patients who undergo both(5). When patients have TURP to treat prostate enlargement after radiotherapy, case studies suggests the risk of incontinence and other complications (e.g. strictures) are higher than TURP before radiotherapy(5). Therefore, for radiotherapy to safely go ahead, outlet obstruction should first be addressed.

UroLift(NeoTract Inc., Pleasanton, CA USA) is a newer, minimally invasive alternative to TURP, approved by the National Institute of Health and Care Excellence (NICE)(6). A growing body of evidence including three meta-analyses supports its use in benign disease(7-9).

There are two randomised control trials (RCTs) for benign disease. The LIFT study conducted in 19 centres across the USA, Canada and Australia designed to evaluate the safety and effectiveness of UroLift in men with Benign Prostate Hyperplasia (BPH) compared to sham. At 12

months, objective, and subjective parameters (urinary symptoms, Quality of Life, and flow rate) were improved in subjects who underwent UroLift, compared to sham(10). The BPH-6 study compared UroLift and TURP with regard to urinary symptoms, recovery experience, sexual function, continence, safety, Quality of Life (QoL), sleep and overall patient perception using a composite endpoint. 80 patients were enrolled across 10 European centres. Improvements were seen in several endpoints in both arms throughout the 2-year follow up(11).

UroLift has not been formally tested in patients undergoing prostate radiotherapy with coexisting urinary tract symptoms. A subgroup analysis performed on retrospective data suggested that patients who had previously undergone prostate radiotherapy experienced symptom relief without an increase in adverse events(12). Extrapolating from the findings of reduced morbidity and recovery time in benign trials, it is likely UroLift could reduce potential treatment delay due to recovery from surgery. Furthermore, the UroLift system could potentially be used as a surrogate for fiducial markers, potentially introducing an efficiency saving(13, 14).

If UroLift is shown to be comparable to TURP for men undergoing radiotherapy, the findings could have an impact on patient choice of treatment, quality of life during and beyond their cancer treatment. UroLift, unlike TURP, can be performed under local anaesthetic and is therefore safer. UroLift has been shown to provide quicker symptom resolution and return to normal activity. Patients can go home on the same day and avoid the need for a catheter afterwards over 70% of the time(11). With healthcare systems still overburdened by the aftermath of Covid-19, a shorter, simpler procedure has attractions for patients, healthcare providers and funders. These benefits need to be balanced against the long-term durability of the procedure.

Data from a NICE-commissioned external assessment centre suggest savings of up to £1,267 per patient with UroLift compared to TURP in benign disease(6). Based on internal estimated

audit figures(15), at least 4,200 patients undergo TURP annually, leading to potential National Health Service (NHS) savings of over £5.3 million per year with UroLift.

Description of treatments

Both TURP and UroLift are well established interventions and widely used for treatment of the enlarged prostate in benign disease with medium to long-term clinical outcome data available(11, 16-18).

TURP is an operation which can be performed under general or regional anaesthetic. A cystoscope is passed into the urethra meatus, along the length of the urethra to the prostate. The obstructing prostate lobes are resected using mono polar or bipolar energy to create a channel for improved urinary flow. Haemostasis is achieved by coagulation followed by insertion of a catheter for irrigation post procedure. Typically, patients stay for 1-2 nights post-operatively and the catheter remains for a variable period.

UroLift can be performed under local anaesthetic, sedation or general anaesthetic. The system comprises of two single-use components, a delivery device and an implant. The implant is made of a nitinol capsular tab, a polyethylene terephthalate monofilament and a stainless-steel end-piece. A modified cystoscope is passed into the urethral meatus, along the length of the urethra to the prostate. The delivery device deploys the implants into the prostate to 'pin' back the lobes of the prostate to create a channel, improving flow. Typically, 2-4 implants are used per patient. In the benign setting, nine out of ten patients do not require a catheter following UroLift.

Research Governance

This trial will be conducted in compliance with the protocol; standard operating procedures, policies, and R&D management guidance of the local trust; Good Clinical Practice (GCP); the UK Policy Framework for Health and Social Care Research; and Medical Devices Regulations 2002.

Aim

The aim is to assess the feasibility of randomising patients in a randomised controlled trial comparing TURP and UroLift and to define the important outcomes to patients that should be used to define treatment success. The results will shape the design of a larger trial that will compare the clinical and cost-effectiveness of the two interventions.

Hypothesis

The hypothesis is that UroLift will deliver clinical outcomes comparable to TURP for the treatment of lower urinary tract symptoms secondary to an enlarged prostate in men undergoing prostate radiotherapy. In addition, UroLift will have additional benefits over TURP in terms of reduced side effects and quicker recovery.

Objectives

Primary Objectives

1. Recruitment - To evaluate whether it is possible to recruit patients to an RCT comparing standard treatment with a new treatment untested in men with prostate cancer.
2. Retention – To assess the proportion of patients who will complete the trial protocol

Secondary Objectives

1. Assess safety and efficacy of UroLift and TURP
2. Determination of patient acceptability of the proposed interventions and Patient Related Outcome Measures (PROMs)
3. Information on costs of the two interventions

Study Design

This trial has been designed with Patient and Public Involvement (PPI). This is a prospective, multi-centre, two-arm, randomised controlled trial. Patients will be recruited from two geographically diverse regions (Southwest London and North Cumbria). Randomisation will be provided by a computer-generated program at the Institute of Cancer Research (ICR) on a 1:1 basis to TURP or UroLift (**Figure 1**).

The randomisation is not blinded; participant and research team will know which treatment pathway has been allocated to the patient.

End Points

Primary Endpoints

The primary endpoints of this study are:

1. Recruitment rate – measured at 3, 6, 9 and 12 months. The target recruitment rate is 3-4 patients per month.
2. Retention rate – anticipate that 80% of patients will complete trial protocol.

Secondary Endpoints

The secondary endpoints of the study are:

1. Acceptability – The Research Team will carry out 12 in-depth interviews. Using the Theoretical Framework of Acceptability(19), affective attitudes, burden, ethicality, intervention coherence, opportunity costs and perceived effectiveness will be assessed.

2. Patient reported outcome measures – These include: Extended Prostate cancer Index Composite-50(EPIC-50)(20, 21), UCLA Prostate Cancer Index (UCLA-PCI)(22), International Consultation of Incontinence Questionnaire -Urinary Incontinence (ICIQ-UI)(23), Euroqol 5D (EQ-5DL)(24, 25), Couples Illness Communication Scale (CICS)(26), International Consultation of Incontinence Questionnaire (PGI-I), International Prostate Symptom Score (IPSS)(27) and Functional Assessment of Cancer Therapy – Prostate (FACT-P)(28). These will be collected at baseline, six weeks and three months post intervention.

3. Health related quality of life validated questionnaires - These will be assessed for appropriateness, usability and completeness for both arms three months post radiotherapy

4. Safety – 30-day surgical morbidity rates will be collected with respect to but not limited to infection, urinary retention, and bleeding.

5. Efficacy of procedure – Improvement in baseline IPSS score and Uroflowmetry (measured by maximum flow rate and post void urine residual).

6. Cost of the two interventions.

7. Re-operation rate for technical failure to reduce outflow obstruction.

In addition, exploratory data will be collected on the following:

1. Prostate Specific Antigen (PSA) – PSA is a surrogate marker for cancer activity and is measured routinely post radiotherapy. TURP typically leads to a reduction in PSA. There is no known evidence on the effect of UroLift on PSA.
2. Time interval between proposed interventions and radiotherapy.

Patient Identification and Recruitment

Sample Size:

The sample size is 45 patients. Recruitment is expected to be completed within 12 months.

Eligibility:

Inclusion Criteria

- Men undergoing prostate radiotherapy for prostate cancer
- Patients with moderate to severe and/or bothersome lower urinary tract symptoms secondary to prostate enlargement (IPSS >8, Quality of Life score ≥3) and/or an obstructive flow rate (Qmax ≤12)
- Patients willing and able to provide written informed consent for the study.

Exclusion Criteria

- Extensive locally advanced disease
- Unfavourable anatomical features (e.g. large middle lobe, for UroLift this requires advanced techniques that have not been fully evaluated in the benign setting)(29)
- Prostates over 100g (as per manufacturer's guidelines)
- Co-morbidities precluding surgery
- Prior prostate cancer treatment (including radical prostatectomy, focal therapy i.e. brachytherapy / high intensity focal ultrasound)
- Prior surgical intervention for benign prostatic hyperplasia (including prior UroLift / TURP / other prostate de-obstructing procedures)
- Urinary symptoms not due to prostatic enlargement as primary cause (i.e. neurological disease)
- Patients with complications of prostate enlargement including catheter dependent retention, recurrent urinary tract infections, bladder stones, obstructive uropathy

- Urinary incontinence due to an incompetent sphincter
- Co-existing gross haematuria
- Current active urinary tract infection

Participants have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the clinician or institution.

Methodology

Treatment Administration

A framework for standardising and delivery of surgical interventions(30). Mandatory, Optional and Prohibited steps of each procedure will be defined by the Trial Management Group (TMG) ahead of recruitment. Fidelity will be checked by more than one independent assessor on the team and further cross- checked.

Transurethral Resection of Prostate

TURP is a well-established procedure, performed to a professionally accredited standard by all surgeons in this study. Standard operating steps will be agreed and followed.

UroLift

UroLift involves the deployment of small permanent implants to widen the otherwise obstructed prostatic urethra and allow relief of symptoms.

The device and system will be used in accordance with the manufacturer's instructions for use.

Treatment Withdrawal

The Principal Investigator(PI) and research team will act in the best interest of patients at all times. Therefore, the PI reserves the right to withdraw treatment at any time e.g., due to a safety concern, a Significant Adverse Event (SAE), if the treatment is no longer warranted, or will cause significant delay to cancer treatment.

Treatment Modification in the Event of Adverse Reaction (AR)

In the event of an unexpected AR, treatment may be withdrawn or modified until the event has stabilised. For example, if a patient planned for UroLift has a mild allergic reaction to local anaesthesia, the procedure may proceed under general anaesthesia once the AR has resolved / stabilised.

PROMS Questionnaires

Patients will be asked to fill in PROMs questionnaires at baseline, Follow Up 1 (6 weeks post-surgery) and Follow Up 2 (3 months post end of radiotherapy). Participants will be approached at their cancer surveillance follow up visits to fill in the research questionnaires on site on a trust encrypted device. The research nurse will explain how to complete the questionnaires and answer any questions. Patients will also be given the option of completing the questionnaires remotely on paper or directly on REDCap within a week of administration. Paper forms returned to the office

will be transcribed onto REDCap by the research nurse at the earliest available opportunity. Data quality will be maintained by periodic cross-referencing by the trial manager and research team.

Health economics

Health economics data and health resource utilisation data will be collected through trial records and the Resource Utilisation Inventory for Economic Evaluation (RUtInE™)(31). RUtInE™ is designed to collect data from both the health care provider perspective following NICE guidelines for cost-effectiveness analysis, but also from the societal perspective with questions accounting for the impact of healthcare options on patients (e.g., out-of-pocket costs), their families and the wider economy.

RUtInE™ will be administered via REDCap / paper, at six months post TURP/UroLift, in line with the other questionnaires in the study at Follow Up 2.

Acceptability interviews

In-depth interviews with a sub-sample of patients to assess acceptability of the interventions will be conducted by a trained research team member.

Three patients will be interviewed at the following timepoints:

- Post randomisation
- Follow up 1 (6 weeks post intervention)
- Follow up 2 (3 months post radiotherapy)

A further three patients who decline to participate / withdraw from the study will also be interviewed to explore the reasons for their decision.

Interviews will be conducted either online or face to face, according to patient preference and the latest Covid-19 policy.

The study opened to recruitment 09/05/2023 and will aim to close on the 09/05/2025.

Data Analysis

10.1 Baseline Assessments

Baseline assessment will be performed at the time of randomisation (**Table 1**). This will include:

- Patient demographics
- Medical History including details of any prior prostate treatment or lower urinary tract surgery
- Physical Examination
- Uroflowmetry including post void residual
- Serum PSA
- Urinalysis
- MRI scan for assessment of prostate size and anatomical suitability for intervention (performed as standard of care)

The following PROMs: EPIC-50, UCLA-PCI, ICIQ-UI, EQ-5DL, CICS, PGI-I and IPSS.

Surgery

Site specific standard care post-operative and discharge pathways will be followed. Surgical morbidity will be recorded up to 30 days following surgery.

Follow Up 1 (6 weeks post-surgery)

The first follow up assessment will take place at six weeks post intervention to ensure patients are fit to proceed to radiotherapy. This will include

- Uroflowmetry
- Physical examination
- Serum PSA
- AE assessment
- PROMs: EPIC-50, UCLA-PCI, ICIQ-UI, EQ-5DL, CICS, PGI-I and IPSS

If symptoms are not yet stable enough to progress to radiotherapy, a further interval assessment will take place four weeks later. Patients who fail to progress with UroLift will be reassessed and offered a TURP if appropriate.

Radiotherapy

Details of the radiotherapy regimen and Radiotherapy Toxicity Oncology Group (RTOG) toxicity data will be collected(32).

Follow Up 2 (3 months post-radiotherapy)

Subsequent assessment will take place at three months post end of radiotherapy. This will include:

- Uroflowmetry
- Physical examination
- Serum PSA
- AE assessment
- PROMS (as per Follow Up 1)
- RUtInE™

Acceptability Interviews

12 In-depth interviews will be conducted in total.

Table 1. Schedule of Enrolment, Interventions and Assessments

				Visit 1	**Visit 2**	**Visit 3**	
	Pre-Randomisation	**Baseline**	**Surgery**	**Follow Up -1 (6 weeks post-surgery)**	**Radiotherapy**	**Follow Up – 2 (3 months post-radiotherapy)**	**Unscheduled**
Screening & Patient	X						

Information Sheet							
Informed Consent	X						
Randomisation		X					
Demographics & Medical History		X					
Physical Examination		X		X		X	
Uroflowmetry and postvoid residual		X		X		X	
Serum PSA		X		X		X	
Urinalysis		X					
PROMs		X		X		X	
Health Economics Questionnaire						X	
UroLift OR TURP			X				
Surgical Morbidity*							X

Adverse Events (including radiotherapy toxicities)		X		X		X	
Radiotherapy					X		
Participant Interview		X#		X#		X#	X$
Protocol Deviations							X
Serious Adverse Events							X

* surgical morbidity will be collected for deaths occurring up to 30 days post-surgery

n=3 patients interviewed post randomisation, at FU1 and FU2

$ n=3 patients interviewed following withdrawal

Data Management

PROMs data will be entered onto REDCap(33, 34), a secure data management platform. The database will be built, tested in accordance to Sponsor approved protocols and managed by MVH and team. The direct research and clinical team will be provided with hierarchical user permissions to access REDCap. All patient email addresses will be stored securely and utilised only for the purposes of distributing the follow-up PROMs questionnaires. PROMs questionnaires can be completed by the patient remotely via an email link, and follow-up data linked to baseline

PROMS information using a unique REDCap ID. The REDCap platform adheres to a nightly back-up schedule and data can be exported in the form of csv and excel files for importing into statistical analysis packages.

Acceptability interviews will be recorded and transcribed with prior patient consent and stored electronically on the Sponsor server.

All electronic records will be held on an encrypted password protected folder accessible on a university / hospital encrypted computer on locked premises. Paper records will be kept onsite on locked premises. Data will be backed up periodically onsite. Electronic and paper files will be stored for five years after study completion before being deleted and securely destroyed.

Recording and Reporting Adverse Events

All Adverse Events (AE) will be recorded, graded and categorised according to Common Terminology Criteria for Adverse Events (CTCAE v5.0).

All SAEs will be reported within 24 hours of the site team becoming aware of the event to the Sponsor. All SAEs will be followed up until event resolution. It is the responsibility of the Sponsor to report all Related Unexpected SAEs (RU-SAE) to REC as appropriate.

Patient and Public Involvement

Patient Reference Group (PRG)

At study conception, a socially and culturally diverse group of patients (who have undergone TURP and radiotherapy) and relatives were brought together to discuss whether this trial addressed an important clinical question. Subsequently, two further group discussions were held; the first was to establish which PROMs to include in this study and a second meeting to assess the method and suitability of data collection. Throughout the design of the study, the PRG were consulted on various aspects including recruitment, consent and timings of the PROMs and interviews. A patient representative participated in the round table discussions and consensus on a stop-go criteria for proceeding to full RCT (**Figure 2**).

The PRG will continue to advise the research team on study methodology and help to identify solutions to barriers. All members are offered training and consent to the Sponsor PPI policies on data protection and patient confidentiality. Meetings will be led by PPI lead (NK) and co-chaired by the patient representative with an anticipation of a total of 8 meetings (6 virtual and 2 face to face).

Trial Management Group (TMG)

A TMG will be appointed from the core team and meet tri-annually/as required to ensure key milestones are met, discuss any safety concerns and develop potential solutions to barriers identified.

Safety Review Committee (SRC)

An independent SRC will meet tri-annually and will overlook the safety and progress of the trial.

Statistical Considerations

Sample size

An estimated sample size calculation was performed based on an expected number of patients who are referred to the sponsor site for radiotherapy each year. Of the 600 patients who have radiotherapy each year, at least half will have symptoms associated with prostate enlargement. An estimate of approximately 90 patients will be eligible for randomisation and that 50% will be successfully randomised (n=45) with a 95% confidence interval of +/-10%.

Similarly, an estimated 80% of patients will complete the trial protocol with a confidence interval of +/-12%.

Analysis Plan

Statistical Analysis

Descriptive analysis on recruitment, randomisation and retention will be conducted on Stata(35). The trial will close to recruitment once the required number of patients have been recruited. Descriptive analyses will include all eligible patients including reasons for patient unwillingness to participate or withdrawal from study. All randomised patients will be further analysed for intended outcomes.

PROMS Analysis

Descriptive analysis is planned for all collected PROMs data. The study has not been powered to detect statistically meaningful differences in PROMs data between the two interventions.

A Delphi process will be held with our PRG to consolidate the PROMs that will be use in a larger scale RCT. The group will help to define the composite endpoint of the study.

Interview Analysis

Thematic analysis will be used to analyse interview transcripts using the Theoretical Framework of Acceptability(19). Thematic analysis of the interview transcripts may reveal aspects of the intervention which require modification at an early stage and will determine whether anticipated acceptability corresponds to experienced acceptability. The same three patients will be interviewed as they progress through the study to capture the depth of their experience and any changes in their perceptions of acceptability over time. In addition, three patients who decide to end their participation in the study will be invited to interview to explore the reasons for their decision. A screening log will capture reasons for patients declining to take part when approached as this will provide some further indication of anticipated acceptability or lack of it.

Health Economics Analysis

Collection of data will enable us to assess response rates to health economics questionnaires, defined as the percentage of patients returning a questionnaire at each time point out of those expected (i.e. not withdrawn or died). It will also help in the development of a future trial protocol for a larger trial which will include a cost-effectiveness analysis in line with NICE guidelines and analysis of patients' out-of-pocket costs associated with their treatment.

Missing or spurious data

Data collection has been designed in accordance with NIHR carbon reduction principles to minimise the risk of missing data. The research nurse and team will be given directed training on completion of all data forms. All missing or spurious data will be queried with the site teams and resolved.

Method of analysis will depend on the amount of missing data, unused or spurious in the study. Missing data may give us insight into questionnaires / parts of questionnaires that patients don't like or find difficult to fill out. All statistical assumptions will be reported. Sensitivity analysis will be performed to test the uncertainty of data parameters.

14.4 Criteria for Early Termination of Trial

An interim review will be done at six months taking into account;

- Recruitment:

  In the event recruitment is exceeded, early termination of the trial will be considered with a view to early progression to a larger RCT

- Stop-go criterion (**Figure 2**):

  If the progression criteria are unlikely to be met, modifications and recommendations will be made following further consultation with the PRG(36).

- Safety:

  Interim analysis demonstrating intervention is harmful or a risk to the patient

- Any other unforeseen circumstances will be documented and reported accordingly

Protocol Deviations

Any deviations from the processes and procedures as outlined in this protocol will be documented and reported to the Sponsor and regulatory bodies.

Patient Confidentiality

All investigators and trial staff will comply with the requirements of the Data Protection Act 2018 and in accordance with the Confidentiality Code of Practice and Data Protection Policy and Procedure.

Consent

Patient consent can be obtained by a trained member of the research team. All members of the research team will have up to date GCP training and adhere to GCP principles in matters related to data handling.

Ethics and Dissemination

The trial has been approved by the South West Frenchay Research Ethics Committee (REC) NHS Health Research Authority (HRA) and Health and Care Research Wales (HCRW). The results will be published in peer-reviewed journals, presented at national meetings and disseminated to patients via social media, charity and hospital websites.

Abbreviations

AE	Adverse Event
AUA	American Urology Association
BADS	British Association of Day Surgery
BOO	Bladder Outflow Obstruction
BPH	Benign Prostate Hyperplasia
CICS	Couples Illness Communication Scale
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
EAU	European Association of Urology
EPIC-50	Expanded Prostate cancer Index Composite –50
EQ5D	Euroqol 5D
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GIRFT	Getting It Right First Time
GP	General Practitioner
ICF	Informed Consent Form
ICIQ	International Consultation of Incontinence Questionnaire
ICR	Institute of Cancer Research
IPSS	International Prostate Symptom Score
ISF	Investigator Site File
LUTS	Lower Urinary Tract Symptoms
MDT	Multidisciplinary Team

1	MRI	Magnetic Resonance Imaging
2	NHS	National Health Service
3	NICE	National Institute for Health and Clinical Excellence
4	NIHR	National Institute for Health Research
5	NPCA	National Prostate Cancer Audit
6	PGI-I	Patient Global Impression of Improvement
7	PI	Principal Investigator
8	PIS	Patient Information Sheet
9	PPI	Patient and Public Involvement
10	PRG	Patient Reference Group
11	PROM	Patient Related Outcome Measure
12	PSA	Prostate Specific Antigen
13	QOL	Quality of Life
14	RCT	Randomised Controlled Trial
15	REC	Research and Ethics Committee
16	RfPB	Research for Patient Benefit
17	R&D	Research and Development
18	RM	Royal Marsden
19	RTOG	Radiation Therapy Oncology Group toxicity criteria
20	RUTINE	Resource Utilisation Inventory for Economic Evaluation
21	SAE	Serious Adverse Event
22	SOP	Standard Operating Procedure
23	TMF	Trial Master File
24	TMG	Trial Management Group
25	TWOC	Trial Without Catheter
26	TURP	Transurethral Resection of Prostate

UCLA-PCI	UCLA Prostate Cancer Index
UI	Urinary incontinence

Figure Legend

Figure 1. Flow diagram of recruitment, randomisation and trial assessment schedule

Figure 2. Stop-go Criteria for progression to full scale RCT

Declarations

Ethics approval and consent to participate

This study is sponsored by the Royal Marsden Hospital. Ethical approval has been granted by the Research Ethics Committee (REC) and Health Research Authority (HRA).

Consent for publication

No individual person's data in any form has been used in this publication.

Availability of data and materials

Only core research team will have access to the final trial dataset. Individual contractual agreements are in place between collaborating organisations and host organisation. Data and materials provided upon request and with permissions.

Competing interests

The authors declare they have no competing interests.

Funding

This project is funded by the NIHR under its Research for Patient Benefit (RfpB) programme (Grant Reference Number NIHR203152). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Authors Contributions

KW/NK/NJ/DN/DC/JS/VK/JW/MM/KG/CM/MVH/RK/CC/EY contributed to the study conceptualisation, methodology, preparation, review and editing of this manuscript. There has been no direct industry input into the study design or manuscript.

KW/NJ/NK/DN/DC/JS/JW/KG/MVH/JW/RK/CC were responsible for acquiring funding to complete the proposed research. CM/MVH built the REDCap database. CM/MVH/EY/KW tested the database according to Sponsor protocol.

KW/NK/NJ/DN/DC/JS/VK/JW/MM/KG/CM/MVH/RK/CC/EY will be involved directly in the study administration, collection of data, analysis and preparation of final manuscript. All authors have reviewed and approved the final submission.

Acknowledgements

We would like to thank Chris Cottrell, our patient representative for his invaluable contributions to the study conception and design. He has participated actively in our TMG meetings including our round table discussions on establishing a stop-go criteria for a larger scale study. We are very grateful to the PRG for helping shape this trial, their invaluable feedback and continued role and support in this research. We would also like to the following people who have given us their time and expertise in helping to obtain funding to make this research possible; David Lowery, Elizabeth Bancroft, Emma Hainsworth and Sofia Georgopolou.

References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol. 1984;132(3):474-9.
2. Welliver C, Feinstein L, Ward JB, Fwu CW, Kirkali Z, Bavendam T, et al. Trends in Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia, 2004 to 2013: the Urologic Diseases in America Project. J Urol. 2020;203(1):171-8.
3. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. Kidney Int. 2006;69(6):1041-7.
4. David R, Buckby A, Kahokehr AA, Lee J, Watson DI, Leung J, et al. Long term genitourinary toxicity following curative intent intensity-modulated radiotherapy for prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2022.
5. Liu M, Pickles T, Berthelet E, Agranovich A, Kwan W, Tyldesley S, et al. Urinary incontinence in prostate cancer patients treated with external beam radiotherapy. Radiother Oncol. 2005;74(2):197-201.
6. National Institute for Health and Clinical Excellence. UroLift for treating lower urinary tract symptoms of benign prostatic hyperplasia 2015 [Available from: https://www.nice.org.uk/guidance/mtg26/chapter/5-Cost-considerations#cost-evidence.
7. Ray A, Morgan HE, Carolan-Rees G. NICE Medical Technologies Guidance [MTG26]: The Urolift system for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia, External Assessment Centre report. 2015.
8. Jung JH, Reddy B, McCutcheon KA, Borofsky M, Narayan V, Kim MH, et al. Prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. Cochrane Database of Systematic Reviews. 2019(5).
9. Perera M, Roberts MJ, Doi SA, Bolton D. 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):704-13.
10. Roehrborn CG, Gange SN, Shore ND, Giddens JL, Bolton DM, Cowan BE, et al. The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. Study. J Urol. 2013;190(6):2161-7.
11. Gratzke C, Barber N, Speakman MJ, Berges R, Wetterauer U, Greene D, et al. Prostatic urethral lift vs transurethral resection of the prostate: 2-year results of the BPH6 prospective, multicentre, randomized study. BJU Int. 2017;119(5):767-75.
12. Eure G, Gange S, Walter P, Khan A, Chabert C, Mueller T, et al. Real-World Evidence of Prostatic Urethral Lift Confirms Pivotal Clinical Study Results: 2-Year Outcomes of a Retrospective Multicenter Study. J Endourol. 2019;33(7):576-84.
13. Biswal NC, Swann B, McKenna MG, Singh R. UroLift as a surrogate for fiducial markers in IGRT planning of prostate cancer in BPH patients. Pract Radiat Oncol. 2018;8(4):e231-e3.
14. Keehn A, Fram E, Garg M, Maria P. UroLift in Place of Fiducial Markers for Patients With Benign Prostatic Hyperplasia Undergoing External Beam Radiation Therapy. Urology. 2017;104:230-4.
15. Holloway N RL, Bosco C, VanHemelrijck M, Seth J, Nitkunan T, Nicol D, Cahill D, Withington J, Kinsella J, Wong K. Management of men with lower urinary tract symptoms referred for prostate radiotherapy. Journal of Clinical Urology. 2022.
16. Reich O, Gratzke C, Stief CG. Techniques and long-term results of surgical procedures for BPH. Eur Urol. 2006;49(6):970-8; discussion 8.
17. Huang SW, Tsai CY, Tseng CS, Shih MC, Yeh YC, Chien KL, et al. Comparative efficacy and safety of new surgical treatments for benign prostatic hyperplasia: systematic review and network meta-analysis. BMJ. 2019;367:l5919.

18. Roehrborn CG, Barkin J, Gange SN, Shore ND, Giddens JL, Bolton DM, et al. Five year results of the prospective randomized controlled prostatic urethral L.I.F.T. study. Can J Urol. 2017;24(3):8802-13.
19. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res. 2017;17(1):88.
20. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology. 2010;76(5):1245-50.
21. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56(6):899-905.
22. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care. 1998;36(7):1002-12.
23. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23(4):322-30.
24. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.
25. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
26. Arden-Close E, Moss-Morris R, Dennison L, Bayne L, Gidron Y. The Couples' Illness Communication Scale (CICS): development and evaluation of a brief measure assessing illness-related couple communication. Br J Health Psychol. 2010;15(Pt 3):543-59.
27. Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, 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):1549-57; discussion 64.
28. Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. 1997;50(6):920-8.
29. Rukstalis D, Grier D, Stroup SP, Tutrone R, deSouza E, Freedman S, et al. Prostatic Urethral Lift (PUL) for obstructive median lobes: 12 month results of the MedLift Study. Prostate Cancer Prostatic Dis. 2019;22(3):411-9.
30. Blencowe N, Mills N, Cook J. Standardising and monitoring the delivery of surgical interventions in randomised controlled trials. British Journal of Surgery. 2016;103:1377-84.
31. Giorgakoudi K. Development of the Resource Utilisation Inventory for Economic Evaluation (RUtInET[M]). Glasgow: NCRI; 2018.
32. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6.
33. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
34. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
35. StataCorp. Stata Statistical Software. 17 ed. College Station, TX StataCorp LLC; 2021.

36. Young HML, Goodliffe S, Madhani M, Phelps K, Regen E, Locke A, et al. Co-producing Progression Criteria for Feasibility Studies: A Partnership between Patient Contributors, Clinicians and Researchers. Int J Environ Res Public Health. 2019;16(19).

Figure 1. Flow diagram of recruitment, randomisation and trial assessment schedule

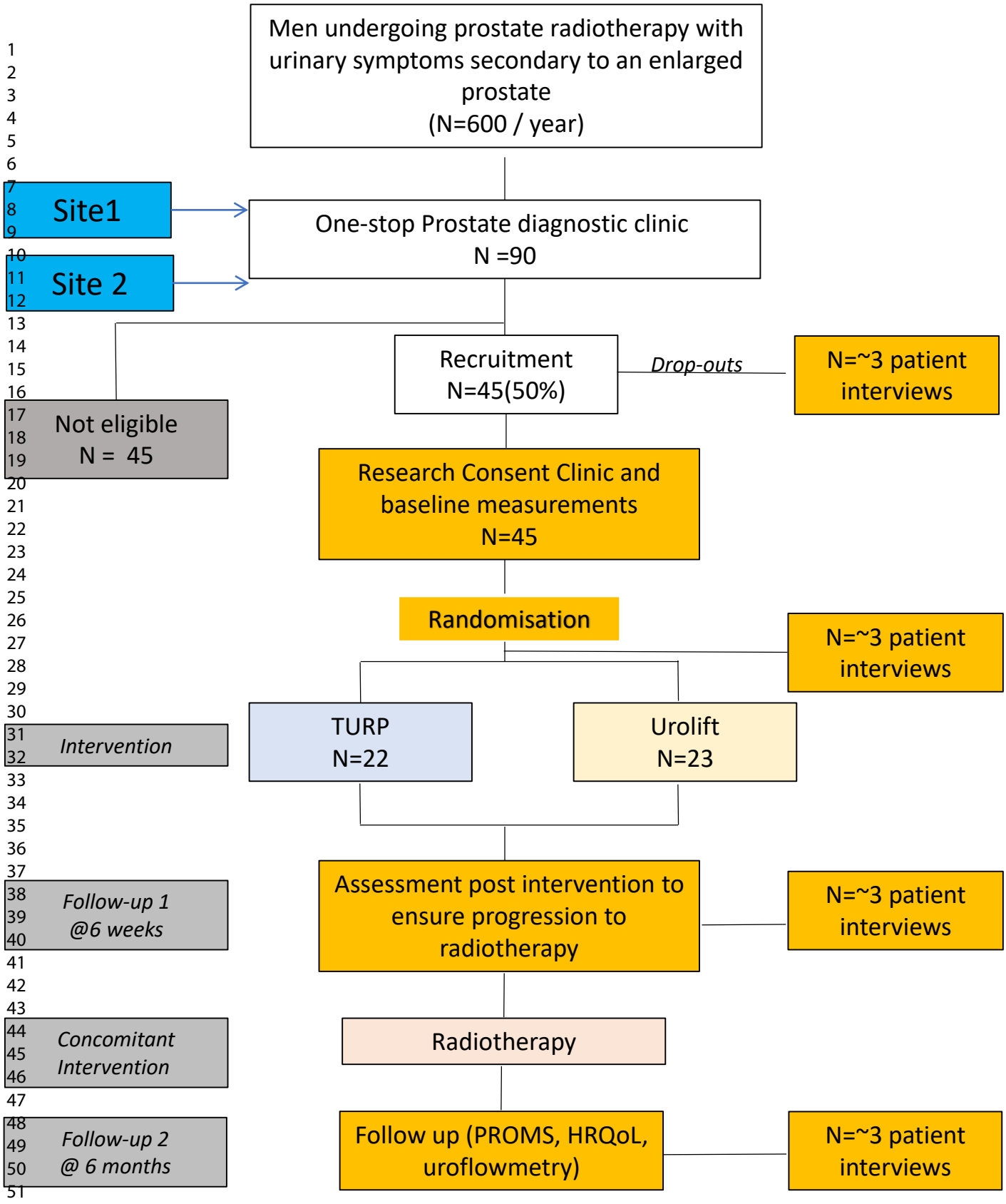

Figure 2. Stop-go Criteria for progression to full scale RCT

Aspect of the trial	Progression Criteria
Eligibility:	**STOP:** 30%
	CHANGE: Expand inclusion criteria e.g. to include T3b, complicated BPH
	GO: 50%
Recruitment:	**STOP:** 15%
	CHANGE: providing access to video material, strategies to promote study to under-served patient groups
	GO: 40%
Intervention acceptability: Whether participants can stick to the intervention	**STOP:** 60%
	CHANGE: longer recovery time, reducing number of PROMS
	GO: 80%
Outcome acceptability: Whether participants can complete the assessments (to be used in RCT) at the start and the end of the study	**STOP:** 40%
	CHANGE: reducing number of PROMS
	GO: 70%
Loss to follow-up: The numbers of participants who drop out or were 'lost' to follow-up.	**STOP:** >35%
	CHANGE: regular study updates, allowing remote follow up where possible
	GO: <25%

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__6_____
	2b	All items from the World Health Organization Trial Registration Data Set	___NA_____
Protocol version	3	Date and version identifier	___1_____
Funding	4	Sources and types of financial, material, and other support	___5,35_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1-4_____
	5b	Name and contact information for the trial sponsor	__4_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___3,4_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___25,36_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	11-12
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	12
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	15, 16
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	16, 17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17,18
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	19-23

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___26_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_17,23-25____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____17-23,27__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____27, 29___

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17,18,23,24
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	26,27
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	26,27
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	28
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	28,29
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	24
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	25
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	35
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	29,

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	29
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	37,38
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	29,37,38
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	35,36
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	35
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	30,31
	31b	Authorship eligibility guidelines and any intended use of professional writers	36
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	37,38
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

A study protocol for a randomised feasibility study **CO**mparing Urolift and **S**tandard **T**ransurethral resection of prostate **A**head of **R**adiotherapy in men with urinary symptoms secondary to prostate enlargement in Southwest London and North Cumbria

COSTAR

Kathie Wong, Netty Kinsella, Jai Seth, David Nicol, Declan Cahill, Ramanathan Kasivisvanathan, John Withington, Masood Moghul, Charlotte L Moss, Mieke Van Hemelrijck, Kyriaki Giorgakoudi, Chris Cottrell, Emma Yates, Vincent Khoo, Nicholas James

Chief Investigator (Corresponding author):	Kathie Wong Consultant Urological Surgeon The Royal Marsden Hospital Fulham Road London SW3 6JJ Kathie.wong2@nhs.net Tel: +44 20 7352 8171
Principal Investigators:	Professor Nicholas James Professor of Prostate and Bladder Cancer Research The Royal Marsden Hospital / Institute of Cancer Research UK Nick.james@icr.ac.uk Mr Jai Seth Consultant Urological Surgeon St Georges University Hospital J.seth@nhs.net Miss Kathie Wong

	Consultant Urological Surgeon North Cumbria Integrated Care Trust
Co-investigators:	Dr Netty Kinsella (PPI lead) Nurse Consultant The Royal Marsden Hospital Netty.kinsella@rmh.nhs.uk Professor David Nicol Chief of Surgery /Consultant Urological Surgeon The Royal Marsden Hospital David.nicol@rmh.nhs.uk Mr Declan Cahill Clinical Lead / Consultant Urological Surgeon The Royal Marsden Hospital Declan.Cahill@rmh.nhs.uk Dr Vincent Khoo Consultant Oncologist The Royal Marsden Hospital / Institute of Cancer Research UK Vincent.Khoo@rmh.nhs.uk Dr Ramanathan Kasivisvanathan Consultant Anaesthetist The Royal Marsden Hospital

	Ramanathan.Kasivisvanathan@rmh.nhs.uk Mr John Withington Consultant Urological Surgeon University College London Gower Street London WC1E 6BT J.withington@ucl.ac.uk Mr Masood Moghul Clinical Research Fellow Royal Marsden Hospital Masood.Moghul@rmh.nhs.uk
Statisticians:	Professor Mieke Van Hemelrijck Professor in Cancer Epidemiology Kings College London Strand London WC2R 2LS Mieke.vanhemelrijck@kcl.ac.uk Charlotte L Moss Database and Project Manager Charlotte.moss@kcl.ac.uk
Health Economist:	Dr Kyriaki Giorgakoudi Senior Health Economist City, University of London Northampton Square, London EC1V 0HB

	NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, UK K.Giorgakoudi@city.ac.uk
Patient Representative:	Chris Cottrell Chris@theexerciseclinic.co.uk
Trial Manager	Emma Yates Clinical Research Operations Manager The Royal Marsden Hospital CO-STAR@rmh.nhs.uk

Sponsor: The Royal Marsden NHS Foundation Trust

Address: The Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ

Site Address:

The Royal Marsden NHS Foundation Trust, Fulham Road, London, SW3 6JJ

The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT

St George's University Hospitals NHS Foundation Trust, Blackshaw Road

Tooting London SW17 0QT

North Cumbria Integrated Care Trust, Newtown Road, Carlisle CA2 7HY

Role of Sponsor:

The Sponsor has responsibility for the legal aspects of the trial, helping to support delivery and provide independent review of the safety and clinical aspects of the trial. The Sponsor is responsible for hosting the trial database.

Funded by the National Institute of Health Research, Research for Patient Benefit grant (NIHR 203152)

~~*Word Count: 3998*~~

Abstract

Introduction

Patients undergoing prostate radiotherapy with an enlarged prostate can have short and long term urinary complications. Currently, Transurethral resection of the prostate (TURP) is the mainstay surgical intervention for men with urinary symptoms due to an enlarged prostate prior to radiotherapy. UroLift (NeoTract Inc., Pleasanton, CA USA) is a recent minimally invasive alternative, widely used in benign disease but is untested in men with prostate cancer.

Methods and Analysis

A multi-centre, two-arm study designed in collaboration with a Patient Reference Group to assess the feasibility of randomising men with prostate cancer and co-existing urinary symptoms due to prostate enlargement to TURP or UroLift ahead of radiotherapy.

45 patients will be enrolled and randomised (1:1) using a computer-generated programme to TURP or UroLift.

Recruitment and retention will be assessed over a 12-month period. Information on clinical outcomes, Adverse Events, and costs will be collected. Clinical outcomes and Patient Reported Outcome Measures (PROMs) will be measured at baseline, six-weeks post-intervention and three months following radiotherapy. A further 12 in-depth interviews will be conducted with a subset of patients to assess acceptability using the Theoretical Framework of Acceptability.

Descriptive analysis on all outcomes will be performed using Stata (StataCorp 2021).

Ethics and Dissemination

The trial has been approved by the Research Ethics Committee (REC) ~~and~~ NHS Health Research Authority (HRA) and Health and Care Research Wales (HCRW). The results will be published in peer-reviewed journals, presented at national meetings and disseminated to patients via social media, charity and hospital websites.

Trial registration IRAS 280225 Clinicaltrials.gov NCT05840549

Keywords

Urolift, transurethral resection of prostate, prostate radiotherapy, prostate cancer, urinary symptoms, bladder outlet obstruction

Strengths and Limitations

- This study is designed in partnership with patients

- Randomisation of patients to the two treatment arms avoids selection bias
- A mixed methods approach allows for maximisation of data collection
- As this is an open label interventional study, it is not possible to blind patients or surgeons to the treatment assigned to patients therefore potentially introducing bias
- This study is a pilot study aimed at assessing feasibility of randomisation and is therefore not powered to detect differences in treatment outcomes

Background

Approximately 14,000 men undergo radical radiotherapy for prostate cancer in England every year, over 85% of men are over 60 years of age and half will have lower urinary tract symptoms (LUTS) secondary to prostatic enlargement(1, 2).

The short-term complications of untreated bladder outlet obstruction from prostatic enlargement in the context of prostate radiotherapy, although rare, can be disastrous, resulting in urinary retention, sepsis and renal failure. In the long-term, urinary symptoms can continue to worsen compounded by the effects of radiotherapy. Transurethral Resection of Prostate (TURP) is the mainstay surgical intervention for outlet obstruction due to prostate enlargement prior to radiotherapy. Studies reporting functional outcomes in patients undergoing TURP and radiotherapy are limited(3, 4). TURP and radiotherapy can both cause incontinence independently and the available evidence suggests a risk of incontinence as high as 27% patients who undergo both(5). When patients have TURP to treat prostate enlargement after radiotherapy, case studies suggests the risk of incontinence and other complications (e.g. strictures) are higher than TURP before radiotherapy(5). Therefore, for radiotherapy to safely go ahead, outlet obstruction should first be addressed.

UroLift(NeoTract Inc., Pleasanton, CA USA) is a newer, minimally invasive alternative to TURP, approved by the National Institute of Health and Care Excellence (NICE)(6). A growing body of evidence including three meta-analyses supports its use in benign disease(7-9).

There are two randomised control trials (RCTs) for benign disease. The LIFT study conducted in 19 centres across the USA, Canada and Australia designed to evaluate the safety and effectiveness of UroLift in men with Benign Prostate Hyperplasia (BPH) compared to sham. At 12

months, objective, and subjective parameters (urinary symptoms, Quality of Life, and flow rate) were improved in subjects who underwent UroLift, compared to sham(10). The BPH-6 study compared UroLift and TURP with regard to urinary symptoms, recovery experience, sexual function, continence, safety, Quality of Life (QoL), sleep and overall patient perception using a composite endpoint. 80 patients were enrolled across 10 European centres. Improvements were seen in several endpoints in both arms throughout the 2-year follow up(11).

UroLift has not been formally tested in patients undergoing prostate radiotherapy with coexisting urinary tract symptoms. A subgroup analysis performed on retrospective data suggested that patients who had previously undergone prostate radiotherapy experienced symptom relief without an increase in adverse events(12). Extrapolating from the findings of reduced morbidity and recovery time in benign trials, it is likely UroLift could reduce potential treatment delay due to recovery from surgery. Furthermore, the UroLift system could potentially be used as a surrogate for fiducial markers, potentially introducing an efficiency saving(13, 14).

If UroLift is shown to be comparable to TURP for men undergoing radiotherapy, the findings could have an impact on patient choice of treatment, quality of life during and beyond their cancer treatment. UroLift, unlike TURP, can be performed under local anaesthetic and is therefore safer. UroLift has been shown to provide quicker symptom resolution and return to normal activity. Patients can go home on the same day and avoid the need for a catheter afterwards over 70% of the time(11). With healthcare systems still overburdened by the aftermath of Covid-19, a shorter, simpler procedure has attractions for patients, healthcare providers and funders. These benefits need to be balanced against the long-term durability of the procedure.

Data from a NICE-commissioned external assessment centre suggest savings of up to £1,267 per patient with UroLift compared to TURP in benign disease(6). Based on internal estimated

audit figures(15), at least 4,200 patients undergo TURP annually, leading to potential National Health Service (NHS) savings of over £5.3 million per year with UroLift.

Description of treatments

Both TURP and UroLift are well established interventions and widely used for treatment of the enlarged prostate in benign disease with medium to long-term clinical outcome data available(11, 16-18).

TURP is an operation which can be performed under general or regional anaesthetic. A cystoscope is passed into the urethra meatus, along the length of the urethra to the prostate. The obstructing prostate lobes are resected using mono polar or bipolar energy to create a channel for improved urinary flow. Haemostasis is achieved by coagulation followed by insertion of a catheter for irrigation post procedure. Typically, patients stay for 1-2 nights post-operatively and the catheter remains for a variable period.

UroLift can be performed under local anaesthetic, sedation or general anaesthetic. The system comprises of two single-use components, a delivery device and an implant. The implant is made of a nitinol capsular tab, a polyethylene terephthalate monofilament and a stainless-steel end-piece. A modified cystoscope is passed into the urethral meatus, along the length of the urethra to the prostate. The delivery device deploys the implants into the prostate to 'pin' back the lobes of the prostate to create a channel, improving flow. Typically, 2-4 implants are used per patient. In the benign setting, nine out of ten patients do not require a catheter following UroLift.

Research Governance

This trial will be conducted in compliance with the protocol; standard operating procedures, policies, and R&D management guidance of the local trust; Good Clinical Practice (GCP); the UK Policy Framework for Health and Social Care Research; and Medical Devices Regulations 2002.

Aim

The aim is to assess the feasibility of randomising patients in a randomised controlled trial comparing TURP and UroLift and to define the important outcomes to patients that should be used to define treatment success. The results will shape the design of a larger trial that will compare the clinical and cost-effectiveness of the two interventions.

Hypothesis

The hypothesis is that UroLift will deliver clinical outcomes comparable to TURP for the treatment of lower urinary tract symptoms secondary to an enlarged prostate in men undergoing prostate radiotherapy. In addition, UroLift will have additional benefits over TURP in terms of reduced side effects and quicker recovery.

Objectives

Primary Objectives

1. Recruitment - To evaluate whether it is possible to recruit patients to an RCT comparing standard treatment with a new treatment untested in men with prostate cancer.
2. Retention – To assess the proportion of patients who will complete the trial protocol

Secondary Objectives

1. Assess safety and efficacy of UroLift and TURP
2. Determination of patient acceptability of the proposed interventions and Patient Related Outcome Measures (PROMs)
3. Information on costs of the two interventions

Study Design

This trial has been designed with Patient and Public Involvement (PPI). This is a prospective, multi-centre, two-arm, randomised controlled trial. Patients will be recruited from two geographically diverse regions (Southwest London and North Cumbria). Randomisation will be provided by a computer-generated program at the Institute of Cancer Research (ICR) on a 1:1 basis to TURP or UroLift (**Figure 1**).

The randomisation is not blinded; participant and research team will know which treatment pathway has been allocated to the patient.

End Points

Primary Endpoints

The primary endpoints of this study are:

1. Recruitment rate – measured at 3, 6, 9 and 12 months. The target recruitment rate is 3-4 patients per month.
2. Retention rate – anticipate that 80% of patients will complete trial protocol.

Secondary Endpoints

The secondary endpoints of the study are:

1. Acceptability – The Research Team will carry out 12 in-depth interviews. Using the Theoretical Framework of Acceptability(19), affective attitudes, burden, ethicality, intervention coherence, opportunity costs and perceived effectiveness will be assessed.

2. Patient reported outcome measures – These include: Extended Prostate cancer Index Composite-50(EPIC-50)(20, 21), UCLA Prostate Cancer Index (UCLA-PCI)(22), International Consultation of Incontinence Questionnaire -Urinary Incontinence (ICIQ-UI)(23), Euroqol 5D (EQ-5DL)(24, 25), Couples Illness Communication Scale (CICS)(26), International Consultation of Incontinence Questionnaire (PGI-I), International Prostate Symptom Score (IPSS)(27) and Functional Assessment of Cancer Therapy – Prostate (FACT-P)(28). These will be collected at baseline, six weeks and three months post intervention.

3. Health related quality of life validated questionnaires - These will be assessed for appropriateness, usability and completeness for both arms three months post radiotherapy

4. Safety – 30-day surgical morbidity rates will be collected with respect to but not limited to infection, urinary retention, and bleeding.

5. Efficacy of procedure – Improvement in baseline IPSS score and Uroflowmetry (measured by maximum flow rate and post void urine residual).

6. Cost of the two interventions.

7. Re-operation rate for technical failure to reduce outflow obstruction.

In addition, exploratory data will be collected on the following:

1. Prostate Specific Antigen (PSA) – PSA is a surrogate marker for cancer activity and is measured routinely post radiotherapy. TURP typically leads to a reduction in PSA. There is no known evidence on the effect of UroLift on PSA.
2. Time interval between proposed interventions and radiotherapy.

Patient Identification and Recruitment

Sample Size:

The sample size is 45 patients. Recruitment is expected to be completed within 12 months.

Eligibility:

Inclusion Criteria

- Men undergoing prostate radiotherapy for prostate cancer
- Patients with moderate to severe and/or bothersome lower urinary tract symptoms secondary to prostate enlargement (IPSS >8, Quality of Life score ≥3) and/or an obstructive flow rate (Qmax ≤12)
- Patients willing and able to provide written informed consent for the study.

Exclusion Criteria

- Extensive locally advanced disease
- Unfavourable anatomical features (e.g. large middle lobe, for UroLift this requires advanced techniques that have not been fully evaluated in the benign setting)(29)
- Prostates over 100g (as per manufacturer's guidelines)
- Co-morbidities precluding surgery
- Prior prostate cancer treatment (including radical prostatectomy, focal therapy i.e. brachytherapy / high intensity focal ultrasound)
- Prior surgical intervention for benign prostatic hyperplasia (including prior UroLift / TURP / other prostate de-obstructing procedures)
- Urinary symptoms not due to prostatic enlargement as primary cause (i.e. neurological disease)
- Patients with complications of prostate enlargement including catheter dependent retention, recurrent urinary tract infections, bladder stones, obstructive uropathy

- Urinary incontinence due to an incompetent sphincter
- Co-existing gross haematuria
- Current active urinary tract infection

Participants have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the clinician or institution.

Methodology

Treatment Administration

A framework for standardising and delivery of surgical interventions(30). Mandatory, Optional and Prohibited steps of each procedure will be defined by the Trial Management Group (TMG) ahead of recruitment. Fidelity will be checked by more than one independent assessor on the team and further cross- checked.

Transurethral Resection of Prostate

TURP is a well-established procedure, performed to a professionally accredited standard by all surgeons in this study. Standard operating steps will be agreed and followed.

UroLift

UroLift involves the deployment of small permanent implants to widen the otherwise obstructed prostatic urethra and allow relief of symptoms.

The device and system will be used in accordance with the manufacturer's instructions for use.

Treatment Withdrawal

The Principal Investigator(PI) and research team will act in the best interest of patients at all times. Therefore, the PI reserves the right to withdraw treatment at any time e.g., due to a safety concern, a Significant Adverse Event (SAE), if the treatment is no longer warranted, or will cause significant delay to cancer treatment.

Treatment Modification in the Event of Adverse Reaction (AR)

In the event of an unexpected AR, treatment may be withdrawn or modified until the event has stabilised. For example, if a patient planned for UroLift has a mild allergic reaction to local anaesthesia, the procedure may proceed under general anaesthesia once the AR has resolved / stabilised.

PROMS Questionnaires

Patients will be asked to fill in PROMs questionnaires at baseline, Follow Up 1 (6 weeks post-surgery) and Follow Up 2 (3 months post end of radiotherapy). Participants will be approached at their cancer surveillance follow up visits to fill in the research questionnaires on site on a trust encrypted device. The research nurse will explain how to complete the questionnaires and answer any questions. Patients will also be given the option of completing the questionnaires remotely on paper or directly on REDCap within a week of administration. Paper forms returned to the office

will be transcribed onto REDCap by the research nurse at the earliest available opportunity. Data quality will be maintained by periodic cross-referencing by the trial manager and research team.

Health economics

Health economics data and health resource utilisation data will be collected through trial records and the Resource Utilisation Inventory for Economic Evaluation (RUtInE™)(31). RUtInE™ is designed to collect data from both the health care provider perspective following NICE guidelines for cost-effectiveness analysis, but also from the societal perspective with questions accounting for the impact of healthcare options on patients (e.g., out-of-pocket costs), their families and the wider economy.

RUtInE™ will be administered via REDCap / paper, at six months post TURP/UroLift, in line with the other questionnaires in the study at Follow Up 2.

Acceptability interviews

In-depth interviews with a sub-sample of patients to assess acceptability of the interventions will be conducted by a trained research team member.

Three patients will be interviewed at the following timepoints:

- Post randomisation
- Follow up 1 (6 weeks post intervention)
- Follow up 2 (3 months post radiotherapy)

A further three patients who decline to participate / withdraw from the study will also be interviewed to explore the reasons for their decision.

Interviews will be conducted either online or face to face, according to patient preference and the latest Covid-19 policy.

The study opened to recruitment 09/05/2023 and will aim to close on the 09/05/2025.

Data Analysis

10.1 Baseline Assessments

Baseline assessment will be performed at the time of randomisation (**Table 1**). This will include:

- Patient demographics
- Medical History including details of any prior prostate treatment or lower urinary tract surgery
- Physical Examination
- Uroflowmetry including post void residual
- Serum PSA
- Urinalysis
- MRI scan for assessment of prostate size and anatomical suitability for intervention (performed as standard of care)

The following PROMs: EPIC-50, UCLA-PCI, ICIQ-UI, EQ-5DL, CICS, PGI-I and IPSS.

Surgery

Site specific standard care post-operative and discharge pathways will be followed. Surgical morbidity will be recorded up to 30 days following surgery.

Follow Up 1 (6 weeks post-surgery)

The first follow up assessment will take place at six weeks post intervention to ensure patients are fit to proceed to radiotherapy. This will include

- Uroflowmetry
- Physical examination
- Serum PSA
- AE assessment
- PROMs: EPIC-50, UCLA-PCI, ICIQ-UI, EQ-5DL, CICS, PGI-I and IPSS

If symptoms are not yet stable enough to progress to radiotherapy, a further interval assessment will take place four weeks later. Patients who fail to progress with UroLift will be reassessed and offered a TURP if appropriate.

Radiotherapy

Details of the radiotherapy regimen and Radiotherapy Toxicity Oncology Group (RTOG) toxicity data will be collected(32).

Follow Up 2 (3 months post-radiotherapy)

Subsequent assessment will take place at three months post end of radiotherapy. This will include:

- Uroflowmetry
- Physical examination
- Serum PSA
- AE assessment
- PROMS (as per Follow Up 1)
- RUtInE™

Acceptability Interviews

12 In-depth interviews will be conducted in total.

Table 1. Schedule of Enrolment, Interventions and Assessments

				Visit 1	**Visit 2**	**Visit 3**	
	Pre-Randomisation	**Baseline**	**Surgery**	**Follow Up -1 (6 weeks post-surgery)**	**Radiotherapy**	**Follow Up – 2 (3 months post-radiotherapy)**	**Unscheduled**
Screening & Patient	X						

Information Sheet							
Informed Consent	X						
Randomisation		X					
Demographics & Medical History		X					
Physical Examination		X		X		X	
Uroflowmetry and postvoid residual		X		X		X	
Serum PSA		X		X		X	
Urinalysis		X					
PROMs		X		X		X	
Health Economics Questionnaire						X	
UroLift OR TURP			X				
Surgical Morbidity*							X

Adverse Events (including radiotherapy toxicities)		X		X		X	
Radiotherapy					X		
Participant Interview		X#		X#		X#	X$
Protocol Deviations							X
Serious Adverse Events							X

* surgical morbidity will be collected for deaths occurring up to 30 days post-surgery

n=3 patients interviewed post randomisation, at FU1 and FU2

$ n=3 patients interviewed following withdrawal

Data Management

PROMs data will be entered onto REDCap(33, 34), a secure data management platform. The database will be built, tested in accordance to Sponsor approved protocols and managed by MVH and team. The direct research and clinical team will be provided with hierarchical user permissions to access REDCap. All patient email addresses will be stored securely and utilised only for the purposes of distributing the follow-up PROMs questionnaires. PROMs questionnaires can be completed by the patient remotely via an email link, and follow-up data linked to baseline

PROMS information using a unique REDCap ID. The REDCap platform adheres to a nightly back-up schedule and data can be exported in the form of csv and excel files for importing into statistical analysis packages.

Acceptability interviews will be recorded and transcribed with prior patient consent and stored electronically on the Sponsor server.

All electronic records will be held on an encrypted password protected folder accessible on a university / hospital encrypted computer on locked premises. Paper records will be kept onsite on locked premises. Data will be backed up periodically onsite. Electronic and paper files will be stored for five years after study completion before being deleted and securely destroyed.

Recording and Reporting Adverse Events

All Adverse Events (AE) will be recorded, graded and categorised according to Common Terminology Criteria for Adverse Events (CTCAE v5.0).

All SAEs will be reported within 24 hours of the site team becoming aware of the event to the Sponsor. All SAEs will be followed up until event resolution. It is the responsibility of the Sponsor to report all Related Unexpected SAEs (RU-SAE) to REC as appropriate.

Patient and Public Involvement

Patient Reference Group (PRG)

At study conception, a socially and culturally diverse group of patients (who have undergone TURP and radiotherapy) and relatives were brought together to discuss whether this trial addressed an important clinical question. Subsequently, two further group discussions were held; the first was to establish which PROMs to include in this study and a second meeting to assess the method and suitability of data collection. Throughout the design of the study, the PRG were consulted on various aspects including recruitment, consent and timings of the PROMs and interviews. A patient representative participated in the round table discussions and consensus on a stop-go criteria for proceeding to full RCT (**Figure 2**).

The PRG will continue to advise the research team on study methodology and help to identify solutions to barriers. All members are offered training and consent to the Sponsor PPI policies on data protection and patient confidentiality. Meetings will be led by PPI lead (NK) and co-chaired by the patient representative with an anticipation of a total of 8 meetings (6 virtual and 2 face to face).

Trial Management Group (TMG)

A TMG will be appointed from the core team and meet tri-annually/as required to ensure key milestones are met, discuss any safety concerns and develop potential solutions to barriers identified.

Safety Review Committee (SRC)

An independent SRC will meet tri-annually and will overlook the safety and progress of the trial.

Statistical Considerations

Sample size

An estimated sample size calculation was performed based on an expected number of patients who are referred to the sponsor site for radiotherapy each year. Of the 600 patients who have radiotherapy each year, at least half will have symptoms associated with prostate enlargement. An estimate of approximately 90 patients will be eligible for randomisation and that 50% will be successfully randomised (n=45) with a 95% confidence interval of +/-10%.

Similarly, an estimated 80% of patients will complete the trial protocol with a confidence interval of +/-12%.

Analysis Plan

Statistical Analysis

Descriptive analysis on recruitment, randomisation and retention will be conducted on Stata(35). The trial will close to recruitment once the required number of patients have been recruited. Descriptive analyses will include all eligible patients including reasons for patient unwillingness to participate or withdrawal from study. All randomised patients will be further analysed for intended outcomes.

PROMS Analysis

Descriptive analysis is planned for all collected PROMs data. The study has not been powered to detect statistically meaningful differences in PROMs data between the two interventions.

A Delphi process will be held with our PRG to consolidate the PROMs that will be use in a larger scale RCT. The group will help to define the composite endpoint of the study.

Interview Analysis

Thematic analysis will be used to analyse interview transcripts using the Theoretical Framework of Acceptability(19). Thematic analysis of the interview transcripts may reveal aspects of the intervention which require modification at an early stage and will determine whether anticipated acceptability corresponds to experienced acceptability. The same three patients will be interviewed as they progress through the study to capture the depth of their experience and any changes in their perceptions of acceptability over time. In addition, three patients who decide to end their participation in the study will be invited to interview to explore the reasons for their decision. A screening log will capture reasons for patients declining to take part when approached as this will provide some further indication of anticipated acceptability or lack of it.

Health Economics Analysis

Collection of data will enable us to assess response rates to health economics questionnaires, defined as the percentage of patients returning a questionnaire at each time point out of those expected (i.e. not withdrawn or died). It will also help in the development of a future trial protocol for a larger trial which will include a cost-effectiveness analysis in line with NICE guidelines and analysis of patients' out-of-pocket costs associated with their treatment.

Missing or spurious data

Data collection has been designed in accordance with NIHR carbon reduction principles to minimise the risk of missing data. The research nurse and team will be given directed training on completion of all data forms. All missing or spurious data will be queried with the site teams and resolved.

Method of analysis will depend on the amount of missing data, unused or spurious in the study. Missing data may give us insight into questionnaires / parts of questionnaires that patients don't like or find difficult to fill out. All statistical assumptions will be reported. Sensitivity analysis will be performed to test the uncertainty of data parameters.

14.4 Criteria for Early Termination of Trial

An interim review will be done at six months taking into account;

- Recruitment:

  In the event recruitment is exceeded, early termination of the trial will be considered with a view to early progression to a larger RCT

- Stop-go criterion (**Figure 2**):

  If the progression criteria are unlikely to be met, modifications and recommendations will be made following further consultation with the PRG(36).

- Safety:

  Interim analysis demonstrating intervention is harmful or a risk to the patient

- Any other unforeseen circumstances will be documented and reported accordingly

Protocol Deviations

Any deviations from the processes and procedures as outlined in this protocol will be documented and reported to the Sponsor and regulatory bodies.

Patient Confidentiality

All investigators and trial staff will comply with the requirements of the Data Protection Act 2018 and in accordance with the Confidentiality Code of Practice and Data Protection Policy and Procedure.

Consent

Patient consent can be obtained by a trained member of the research team. All members of the research team will have up to date GCP training and adhere to GCP principles in matters related to data handling.

Ethics and Dissemination

The trial has been approved by the Research Ethics Committee (REC) NHS Health Research Authority (HRA) and Health and Care Research Wales (HCRW). The results will be published in peer-reviewed journals, presented at national meetings and disseminated to patients via social media, charity and hospital websites.

~~Discussion~~

~~In most men undergoing prostate radiotherapy, symptoms will be due to benign components of the gland, potentially exacerbated by co-existent tumour. Thus there is a reasonable expectation that a technique designed for use in the benign setting will be effective in men with cancer. As most men having prostate radiotherapy generally have good oncological outcomes, there has been a shift in clinical focus in the last decade to survivorship beyond cancer treatment.~~

~~Currently, the standard surgical treatment for men with urinary symptoms ahead of prostate radiotherapy is TURP. However, there are concerns regarding the long-term consequence of tissue damage from the combined effects of surgery and radiotherapy.~~

~~Should UroLift be shown to have comparable clinical outcomes and safety to TURP, this trial will provide early evidence for its use in these patients. In addition to the benefits of avoiding regional or general anaesthetic and quicker recovery, there are wider healthcare resource and cost-saving benefits which will be evaluated in a larger multicentred, multi-arm trial.~~

~~The trial has been designed to facilitate patient participation with special consideration given to social and cultural inclusivity. The participants will be recruited from two contrasting regions of the UK; Northwest Cumbria has the highest rates of poverty, unemployment, poor health and deaths in England whilst London has the largest ethnically diverse population. To ensure matters of equality, diversity and inclusion are proactively considered, this will be a standing item on the agenda for all study management and governance groups.~~

~~A two-stage round table discussion involving the core team and a patient representative was held to determine the stop-go criteria for proceeding to a larger multicentre RCT applying a Nominal Group Technique(36) (**Figure 2**).~~

~~At the end of the study, the team hope to understand whether such a trial is acceptable to all stakeholders, is methodologically robust and feasible. Key findings of this study will be published in peer-reviewed journals, presented at national meetings and disseminated to patients via social media, charity and trust websites. The findings of this study will add new evidence to current limited literature on this subject and help men in the future to make informed decisions about their prostate cancer treatment options.~~

Abbreviations

AE	Adverse Event
AUA	American Urology Association
BADS	British Association of Day Surgery
BOO	Bladder Outflow Obstruction
BPH	Benign Prostate Hyperplasia
CICS	Couples Illness Communication Scale
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
EAU	European Association of Urology
EPIC-50	Expanded Prostate cancer Index Composite –50
EQ5D	Euroqol 5D
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GIRFT	Getting It Right First Time
GP	General Practitioner
ICF	Informed Consent Form
ICIQ	International Consultation of Incontinence Questionnaire
ICR	Institute of Cancer Research
IPSS	International Prostate Symptom Score
ISF	Investigator Site File
LUTS	Lower Urinary Tract Symptoms
MDT	Multidisciplinary Team

1	MRI	Magnetic Resonance Imaging
2	NHS	National Health Service
3	NICE	National Institute for Health and Clinical Excellence
4	NIHR	National Institute for Health Research
5	NPCA	National Prostate Cancer Audit
6	PGI-I	Patient Global Impression of Improvement
7	PI	Principal Investigator
8	PIS	Patient Information Sheet
9	PPI	Patient and Public Involvement
10	PRG	Patient Reference Group
11	PROM	Patient Related Outcome Measure
12	PSA	Prostate Specific Antigen
13	QOL	Quality of Life
14	RCT	Randomised Controlled Trial
15	REC	Research and Ethics Committee
16	RfPB	Research for Patient Benefit
17	R&D	Research and Development
18	RM	Royal Marsden
19	RTOG	Radiation Therapy Oncology Group toxicity criteria
20	RUTINE	Resource Utilisation Inventory for Economic Evaluation
21	SAE	Serious Adverse Event
22	SOP	Standard Operating Procedure
23	TMF	Trial Master File
24	TMG	Trial Management Group
25	TWOC	Trial Without Catheter
26	TURP	Transurethral Resection of Prostate

UCLA-PCI	UCLA Prostate Cancer Index
UI	Urinary incontinence

Figure Legend

Figure 1. Flow diagram of recruitment, randomisation and trial assessment schedule

Figure 2. Stop-go Criteria for progression to full scale RCT

Declarations

Ethics approval and consent to participate

This study is sponsored by the Royal Marsden Hospital. Ethical approval has been granted by the Research Ethics Committee (REC) and Health Research Authority (HRA).

Consent for publication

No individual person's data in any form has been used in this publication.

Availability of data and materials

Only core research team will have access to the final trial dataset. Individual contractual agreements are in place between collaborating organisations and host organisation. Data and materials provided upon request and with permissions.

Competing interests

The authors declare they have no competing interests.

Funding

This project is funded by the NIHR under its Research for Patient Benefit (RfpB) programme (Grant Reference Number NIHR203152). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Authors Contributions

KW/NK/NJ/DN/DC/JS/VK/JW/MM/KG/CM/MVH/RK/CC/EY contributed to the study conceptualisation, methodology, preparation, review and editing of this manuscript. There has been no direct industry input into the study design or manuscript.

KW/NJ/NK/DN/DC/JS/JW/KG/MVH/JW/RK/CC were responsible for acquiring funding to complete the proposed research. CM/MVH built the REDCap database. CM/MVH/EY/KW tested the database according to Sponsor protocol.

KW/NK/NJ/DN/DC/JS/VK/JW/MM/KG/CM/MVH/RK/CC/EY will be involved directly in the study administration, collection of data, analysis and preparation of final manuscript. All authors have reviewed and approved the final submission.

Acknowledgements

We would like to thank Chris Cottrell, our patient representative for his invaluable contributions to the study conception and design. He has participated actively in our TMG meetings including our round table discussions on establishing a stop-go criteria for a larger scale study. We are very grateful to the PRG for helping shape this trial, their invaluable feedback and continued role and support in this research. We would also like to the following people who have given us their time and expertise in helping to obtain funding to make this research possible; David Lowery, Elizabeth Bancroft, Emma Hainsworth and Sofia Georgopolou.

Appendix 1 – Trial Consent Form

CONSENT FORM

CO-STAR

A randomised feasibility study **CO**mparing Urolift and **S**tandard **T**ransurethral resection of prostate **A**head of **R**adiotherapy in men with urinary symptoms secondary to prostate enlargement

Patient Study ID		**Principal Investigator**	

Please initial each statement if you agree with the following statements

1	I confirm that I have read the Patient Information Sheet Version....., dated ..... for the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
3	I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from The Royal Marsden NHS Foundation Trust, where it is relevant to my taking part in this research study. I give permission for these individuals to access my records and understand that my confidentiality will be maintained.	
4	I agree that should my clinical care require me to attend different hospitals for my information to be shared across the hospitals participating in this research to facilitate my participation in the study.	
5	I understand that the information collected about me may be used to support other research in the future and may be shared anonymously with other researchers.	
6	I agree to my General Practitioner being informed of my participation in the study.	
7	I agree to take part in the above study.	

Please initial 'yes' or 'no' for the following statements

Yes	No

7	I agree to participate in the interviews as described in the Patient Information Sheet (Interviews) Version....., dated ..... for the above study		
8	I agree for anonymised quotes taken from my interview transcripts to be used in publications and presentations about this study		
9	I agree to provide my email address and give permission to be contacted by email with a unique URL so that I can access the relevant questionnaires for the study and also to be sent reminders to complete these questionnaires as necessary. The questionnaires will be distributed by a third-party website (GDPR compliant). Please let us know if you would prefer paper copies instead.		

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

References

1. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol. 1984;132(3):474-9.
2. Welliver C, Feinstein L, Ward JB, Fwu CW, Kirkali Z, Bavendam T, et al. Trends in Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia, 2004 to 2013: the Urologic Diseases in America Project. J Urol. 2020;203(1):171-8.
3. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. Kidney Int. 2006;69(6):1041-7.
4. David R, Buckby A, Kahokehr AA, Lee J, Watson DI, Leung J, et al. Long term genitourinary toxicity following curative intent intensity-modulated radiotherapy for prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2022.
5. Liu M, Pickles T, Berthelet E, Agranovich A, Kwan W, Tyldesley S, et al. Urinary incontinence in prostate cancer patients treated with external beam radiotherapy. Radiother Oncol. 2005;74(2):197-201.
6. National Institute for Health and Clinical Excellence. UroLift for treating lower urinary tract symptoms of benign prostatic hyperplasia 2015 [Available from: https://www.nice.org.uk/guidance/mtg26/chapter/5-Cost-considerations#cost-evidence.
7. Ray A, Morgan HE, Carolan-Rees G. NICE Medical Technologies Guidance [MTG26]: The Urolift system for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia, External Assessment Centre report. 2015.
8. Jung JH, Reddy B, McCutcheon KA, Borofsky M, Narayan V, Kim MH, et al. Prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. Cochrane Database of Systematic Reviews. 2019(5).
9. Perera M, Roberts MJ, Doi SA, Bolton D. 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):704-13.
10. Roehrborn CG, Gange SN, Shore ND, Giddens JL, Bolton DM, Cowan BE, et al. The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. Study. J Urol. 2013;190(6):2161-7.
11. Gratzke C, Barber N, Speakman MJ, Berges R, Wetterauer U, Greene D, et al. Prostatic urethral lift vs transurethral resection of the prostate: 2-year results of the BPH6 prospective, multicentre, randomized study. BJU Int. 2017;119(5):767-75.
12. Eure G, Gange S, Walter P, Khan A, Chabert C, Mueller T, et al. Real-World Evidence of Prostatic Urethral Lift Confirms Pivotal Clinical Study Results: 2-Year Outcomes of a Retrospective Multicenter Study. J Endourol. 2019;33(7):576-84.
13. Biswal NC, Swann B, McKenna MG, Singh R. UroLift as a surrogate for fiducial markers in IGRT planning of prostate cancer in BPH patients. Pract Radiat Oncol. 2018;8(4):e231-e3.
14. Keehn A, Fram E, Garg M, Maria P. UroLift in Place of Fiducial Markers for Patients With Benign Prostatic Hyperplasia Undergoing External Beam Radiation Therapy. Urology. 2017;104:230-4.
15. Holloway N RL, Bosco C, VanHemelrijck M, Seth J, Nitkunan T, Nicol D, Cahill D, Withington J, Kinsella J, Wong K. Management of men with lower urinary tract symptoms referred for prostate radiotherapy. Journal of Clinical Urology. 2022.
16. Reich O, Gratzke C, Stief CG. Techniques and long-term results of surgical procedures for BPH. Eur Urol. 2006;49(6):970-8; discussion 8.
17. Huang SW, Tsai CY, Tseng CS, Shih MC, Yeh YC, Chien KL, et al. Comparative efficacy and safety of new surgical treatments for benign prostatic hyperplasia: systematic review and network meta-analysis. BMJ. 2019;367:l5919.

18. Roehrborn CG, Barkin J, Gange SN, Shore ND, Giddens JL, Bolton DM, et al. Five year results of the prospective randomized controlled prostatic urethral L.I.F.T. study. Can J Urol. 2017;24(3):8802-13.
19. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res. 2017;17(1):88.
20. Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology. 2010;76(5):1245-50.
21. Wei JT, Dunn RL, Litwin MS, Sandler HM, Sanda MG. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;56(6):899-905.
22. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care. 1998;36(7):1002-12.
23. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23(4):322-30.
24. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.
25. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
26. Arden-Close E, Moss-Morris R, Dennison L, Bayne L, Gidron Y. The Couples' Illness Communication Scale (CICS): development and evaluation of a brief measure assessing illness-related couple communication. Br J Health Psychol. 2010;15(Pt 3):543-59.
27. Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, 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):1549-57; discussion 64.
28. Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology. 1997;50(6):920-8.
29. Rukstalis D, Grier D, Stroup SP, Tutrone R, deSouza E, Freedman S, et al. Prostatic Urethral Lift (PUL) for obstructive median lobes: 12 month results of the MedLift Study. Prostate Cancer Prostatic Dis. 2019;22(3):411-9.
30. Blencowe N, Mills N, Cook J. Standardising and monitoring the delivery of surgical interventions in randomised controlled trials. British Journal of Surgery. 2016;103:1377-84.
31. Giorgakoudi K. Development of the Resource Utilisation Inventory for Economic Evaluation (RUtInET[M]). Glasgow: NCRI; 2018.
32. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6.
33. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
34. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
35. StataCorp. Stata Statistical Software. 17 ed. College Station, TX StataCorp LLC; 2021.

36. Young HML, Goodliffe S, Madhani M, Phelps K, Regen E, Locke A, et al. Co-producing Progression Criteria for Feasibility Studies: A Partnership between Patient Contributors, Clinicians and Researchers. Int J Environ Res Public Health. 2019;16(19).