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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 (CO-STAR): a study protocol for a randomised feasibility study

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ABSTRACT

Introduction Patients undergoing prostate radiotherapy with an enlarged prostate can have short-term 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, 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 multicentre, two-arm study designed in collaboration with a Patient Reference Group to assess the feasibility of randomising men with prostate cancer and coexisting 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 will be measured at baseline, 6 weeks postintervention and 3 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 V.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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ 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.

Trial registration number NCT05840549.

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 the 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 suggest that the risk of incontinence and other complications (eg, strictures) are higher than TURP before radiotherapy.[5] Therefore, for radiotherapy to safely go ahead, outlet obstruction should first be addressed.

UroLift (NeoTract, 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 with sham. At 12 months, objective and subjective parameters (urinary symptoms, quality of life (QoL) and flow rate) were improved in subjects who underwent UroLift, compared with sham.[10] The BPH-6 study compared UroLift and TURP with regard to urinary symptoms, recovery experience, sexual function, continence, safety, QoL, sleep and overall patient perception using a composite endpoint. Of note, 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 (AE).[12] Extrapolating from the findings of reduced morbidity and recovery time in benign trials, it is likely that 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, QoL 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 £1267 per patient with UroLift compared with TURP in benign disease.[6] Based on internal estimated audit figures,[15] at least 4200 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 postoperatively 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 10 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 RCT 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 with TURP for the treatment of

LUTS 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—o 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, multicentre, two-arm, RCT. Patients will be recruited from two geographically diverse regions (Southwest London and North Cumbria). Randomisation will be provided by a computer-generated programme 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 as :

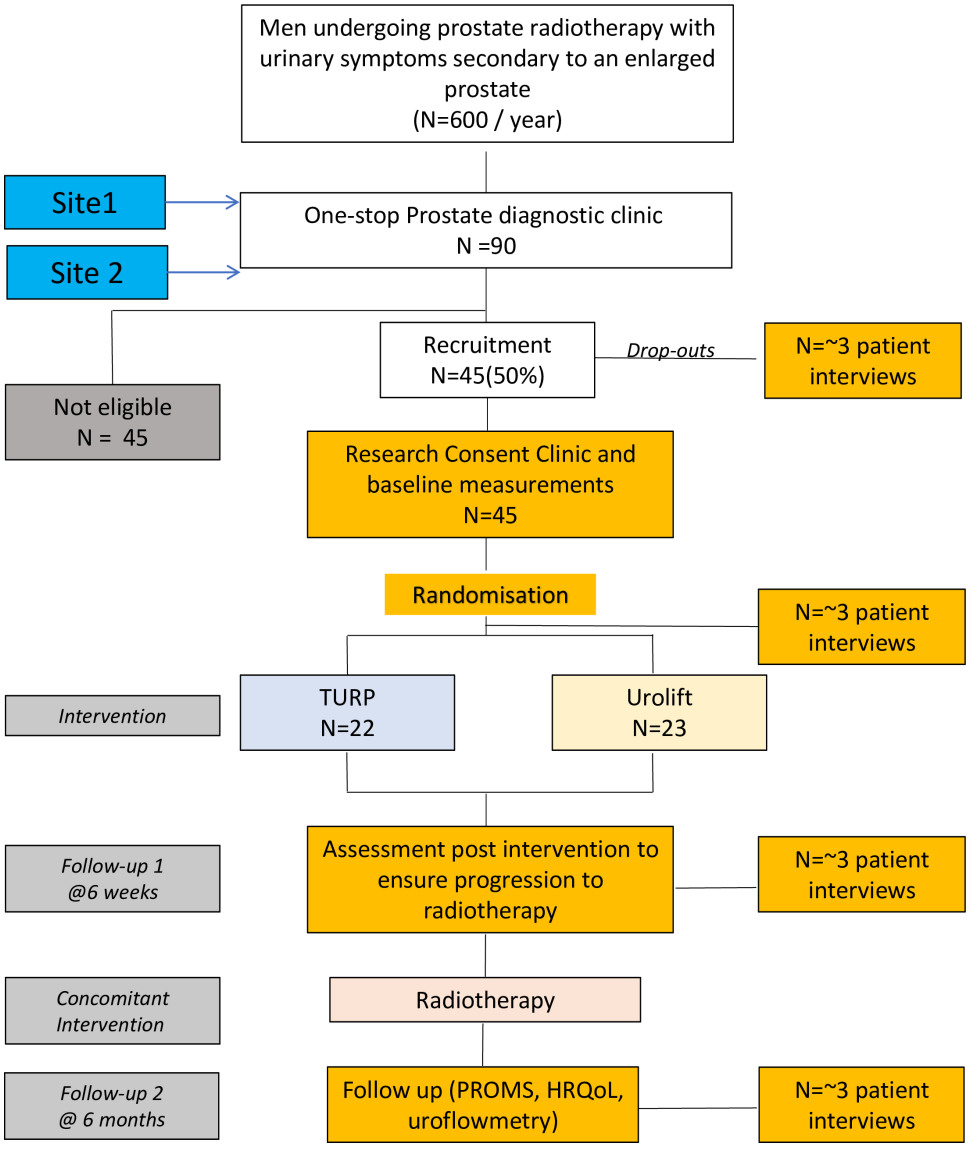

Figure 1 Flow diagram of recruitment, randomisation and trial assessment schedule. HRQoL, health-related quality of life; PROMs, patient reported outcome measures; TURP, transurethral resection of the prostate.

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, 6 weeks and 3 months post radiotherapy.
3. Health-related QoL validated questionnaires—these will be assessed for appropriateness, usability and completeness for both arms 3 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. Reoperation 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 LUTS secondary to prostate enlargement (IPSS>8, QoL 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 (eg, 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, ie, brachytherapy/high intensity focal ultrasound).
- Prior surgical intervention for benign prostatic hyperplasia (including prior UroLift/TURP/other prostate deobstructing procedures).
- Urinary symptoms not due to prostatic enlargement as primary cause (ie, 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.
- Coexisting 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

for example, 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 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 Research Electronic Data Capture (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 healthcare 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 (eg, out-of-pocket costs), their families and the wider economy.

RUtInE™ will be administered via REDCap/paper, at 6 months post TURP/UroLift, in line with the other questionnaires in the study at follow-up 2.

Acceptability interviews

In-depth interviews with a subsample 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 9 May 2023 and will aim to close on 9 May 2025.

Data analysis

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 postvoid residual
- Serum PSA
- Urinalysis
- MRI scan for assessment of prostate size and anatomical suitability for intervention (performed as standard of care)

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

Surgery

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

Follow-up 1 (6 weeks postsurgery)

The first follow-up assessment will take place at 6 weeks post intervention to ensure patients are fit to proceed to radiotherapy. This will include the following:

- 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 4 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 postradiotherapy)

Subsequent assessment will take place at 3 months post radiotherapy. This will include:

- Uroflowmetry
- Physical examination
- Serum PSA
- AE assessment
- PROMs (as per follow-up 1).
- RUtInE™.

Acceptability interviews

Twelve n-depth interviews will be conducted in total.

Table 1 Schedule of enrolment, interventions and assessments

				Visit 1	Visit 2	Visit 3	
	Prerandomisation	Baseline	Surgery	Follow-up-1 (6 weeks postsurgery)	Radiotherapy	Follow-up-2 (3 months postradiotherapy)	Unscheduled
Screening and patient information sheet	X						
Informed consent	X						
Randomisation		X					
Demographics and 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 postsurgery.
†n=3 patients interviewed post randomisation, at FU1 and FU2.
‡n=3 patients interviewed following withdrawal.
FU, follow-up; PROMs, patient-reported outcome measures; PSAs, prostate-specific antigen; TURP, transurethral resection of the prostate.

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 5 years after study completion before being deleted and securely destroyed.

Recording and reporting adverse events

All AE will be recorded, graded and categorised according to Common Terminology Criteria for Adverse Events (CTCAE V.5.0).

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

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%

Figure 2 Stop-go criteria for progression to full scale RCT. RCT, randomised controlled trials.

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 cochaired by the patient representative with an anticipation of a total of eight meetings (6 virtual and two face to face).

Trial management group (TMG)

A TMG will be appointed from the core team and meet triannually/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 triannually 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% CI of ±10%.

Similarly, an estimated 80% of patients will complete the trial protocol with a CI 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 (ie, 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 an insight into questionnaires/parts of questionnaires that patients do not 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.

Criteria for early termination of trial

An interim review will be done at 6 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.

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