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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).**

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

COSTAR

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15 Role of Sponsor:

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

4
5 Funded by the National Institute of Health Research, Research for Patient Benefit grant (NIHR
6 203152)

7 8 **Abstract**

9 10 **Introduction**

11
12 Patients undergoing prostate radiotherapy with an enlarged prostate can have short and long
13 term urinary complications. Currently, Transurethral resection of the prostate (TURP) is the
14 mainstay surgical intervention for men with urinary symptoms due to an enlarged prostate prior
15 to radiotherapy. UroLift (NeoTract Inc., Pleasanton, CA USA) is a recent minimally invasive
16 alternative, widely used in benign disease but is untested in men with prostate cancer.

17 18 **Methods and Analysis**

19
20 A multi-centre, two-arm study designed in collaboration with a Patient Reference Group to assess
21 the feasibility of randomising men with prostate cancer and co-existing urinary symptoms due to
22 prostate enlargement to TURP or UroLift ahead of radiotherapy.

23
24 45 patients will be enrolled and randomised (1:1) using a computer-generated programme to
25 TURP or UroLift.

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

6
7 Descriptive analysis on all outcomes will be performed using Stata (StataCorp 2021).
8
9

10 **Ethics and Dissemination**

11 The trial has been approved by the Research Ethics Committee (REC) NHS Health Research
12 Authority (HRA) and Health and Care Research Wales (HCRW). The results will be published in
13 peer-reviewed journals, presented at national meetings and disseminated to patients via social
14 media, charity and hospital websites.
15

16 **Trial registration IRAS 280225 Clinicaltrials.gov NCT05840549**

17 **Keywords**

18
19
20 Urolift, transurethral resection of prostate, prostate radiotherapy, prostate cancer, urinary
21 symptoms, bladder outlet obstruction
22

23 **Strengths and Limitations**

- 24
25 • This study is designed in partnership with patients
- 26 • Randomisation of patients to the two treatment arms avoids selection bias

- 1
- 2 1 • A mixed methods approach allows for maximisation of data collection
- 3
- 4 2 • As this is an open label interventional study, it is not possible to blind patients or
- 5
- 6 3 surgeons to the treatment assigned to patients therefore potentially introducing bias
- 7
- 8 4 • This study is a pilot study aimed at assessing feasibility of randomisation and is
- 9
- 10 5 therefore not powered to detect differences in treatment outcomes
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For peer review only

1 Background

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5
6 Approximately 14,000 men undergo radical radiotherapy for prostate cancer in England every
7
8 year, over 85% of men are over 60 years of age and half will have lower urinary tract symptoms
9
10 (LUTS) secondary to prostatic enlargement(1, 2).

11
12
13
14 The short-term complications of untreated bladder outlet obstruction from prostatic enlargement
15
16 in the context of prostate radiotherapy, although rare, can be disastrous, resulting in urinary
17
18 retention, sepsis and renal failure. In the long-term, urinary symptoms can continue to worsen
19
20 compounded by the effects of radiotherapy. Transurethral Resection of Prostate (TURP) is the
21
22 mainstay surgical intervention for outlet obstruction due to prostate enlargement prior to
23
24 radiotherapy. Studies reporting functional outcomes in patients undergoing TURP and
25
26 radiotherapy are limited(3, 4). TURP and radiotherapy can both cause incontinence independently
27
28 and the available evidence suggests a risk of incontinence as high as 27% patients who undergo
29
30 both(5). When patients have TURP to treat prostate enlargement after radiotherapy, case studies
31
32 suggests the risk of incontinence and other complications (e.g. strictures) are higher than TURP
33
34 before radiotherapy(5). Therefore, for radiotherapy to safely go ahead, outlet obstruction should
35
36 first be addressed.
37
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40
41
42 UroLift(NeoTract Inc., Pleasanton, CA USA) is a newer, minimally invasive alternative to TURP,
43
44 approved by the National Institute of Health and Care Excellence (NICE)(6). A growing body of
45
46 evidence including three meta-analyses supports its use in benign disease(7-9).
47
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49

50
51 There are two randomised control trials (RCTs) for benign disease. The LIFT study conducted in
52
53 19 centres across the USA, Canada and Australia designed to evaluate the safety and
54
55 effectiveness of UroLift in men with Benign Prostate Hyperplasia (BPH) compared to sham. At 12

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

7
8 UroLift has not been formally tested in patients undergoing prostate radiotherapy with coexisting
9 urinary tract symptoms. A subgroup analysis performed on retrospective data suggested that
10 patients who had previously undergone prostate radiotherapy experienced symptom relief without
11 an increase in adverse events(12). Extrapolating from the findings of reduced morbidity and
12 recovery time in benign trials, it is likely UroLift could reduce potential treatment delay due to
13 recovery from surgery. Furthermore, the UroLift system could potentially be used as a surrogate
14 for fiducial markers, potentially introducing an efficiency saving(13, 14).

15
16 If UroLift is shown to be comparable to TURP for men undergoing radiotherapy, the findings could
17 have an impact on patient choice of treatment, quality of life during and beyond their cancer
18 treatment. UroLift, unlike TURP, can be performed under local anaesthetic and is therefore safer.
19 UroLift has been shown to provide quicker symptom resolution and return to normal activity.
20 Patients can go home on the same day and avoid the need for a catheter afterwards over 70% of
21 the time(11). With healthcare systems still overburdened by the aftermath of Covid-19, a shorter,
22 simpler procedure has attractions for patients, healthcare providers and funders. These benefits
23 need to be balanced against the long-term durability of the procedure.

24
25 Data from a NICE-commissioned external assessment centre suggest savings of up to £1,267
26 per patient with UroLift compared to TURP in benign disease(6). Based on internal estimated

1
2 1 audit figures(15), at least 4,200 patients undergo TURP annually, leading to potential National
3
4 2 Health Service (NHS) savings of over £5.3 million per year with UroLift.
5
6 3

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8 4 *Description of treatments*
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10 5
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12 6 Both TURP and UroLift are well established interventions and widely used for treatment of the
13
14 7 enlarged prostate in benign disease with medium to long-term clinical outcome data available(11,
15
16 8 16-18).
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18 9

19
20
21 10 TURP is an operation which can be performed under general or regional anaesthetic. A
22
23 11 cystoscope is passed into the urethra meatus, along the length of the urethra to the prostate. The
24
25 12 obstructing prostate lobes are resected using mono polar or bipolar energy to create a channel
26
27 13 for improved urinary flow. Haemostasis is achieved by coagulation followed by insertion of a
28
29 14 catheter for irrigation post procedure. Typically, patients stay for 1-2 nights post-operatively and
30
31 15 the catheter remains for a variable period.
32
33 16

34
35 17 UroLift can be performed under local anaesthetic, sedation or general anaesthetic. The system
36
37 18 comprises of two single-use components, a delivery device and an implant. The implant is made
38
39 19 of a nitinol capsular tab, a polyethylene terephthalate monofilament and a stainless-steel end-
40
41 20 piece. A modified cystoscope is passed into the urethral meatus, along the length of the urethra
42
43 21 to the prostate. The delivery device deploys the implants into the prostate to 'pin' back the lobes
44
45 22 of the prostate to create a channel, improving flow. Typically, 2-4 implants are used per patient.
46
47 23 In the benign setting, nine out of ten patients do not require a catheter following UroLift.
48
49 24

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52 25 *Research Governance*
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54 26

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

5 **Aim**

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

12 **Hypothesis**

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

18 **Objectives**

20 *Primary Objectives*

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

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4 2 *Secondary Objectives*
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8 4 1. Assess safety and efficacy of UroLift and TURP
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10 5 2. Determination of patient acceptability of the proposed interventions and Patient Related
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12 6 Outcome Measures (PROMs)
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15 7 3. Information on costs of the two interventions
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21 9 **Study Design**

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26 11 This trial has been designed with Patient and Public Involvement (PPI). This is a prospective,
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28 12 multi-centre, two-arm, randomised controlled trial. Patients will be recruited from two
29
30 13 geographically diverse regions (Southwest London and North Cumbria). Randomisation will be
31
32 14 provided by a computer-generated program at the Institute of Cancer Research (ICR) on a 1:1
33
34 15 basis to TURP or UroLift (**Figure 1**).
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39 17 The randomisation is not blinded; participant and research team will know which treatment
40
41 18 pathway has been allocated to the patient.
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46 20 **End Points**

47 48 21 49 50 22 *Primary Endpoints*

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52 23
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55 24 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

- 1
- 2 1 4. Safety – 30-day surgical morbidity rates will be collected with respect to but not limited to
- 3
- 4 2 infection, urinary retention, and bleeding.
- 5
- 6 3
- 7
- 8 4 5. Efficacy of procedure – Improvement in baseline IPSS score and Uroflowmetry
- 9
- 10 5 (measured by maximum flow rate and post void urine residual).
- 11
- 12 6
- 13
- 14 7 6. Cost of the two interventions.
- 15
- 16 8
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- 18 9 7. Re-operation rate for technical failure to reduce outflow obstruction.
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- 20
- 21 10
- 22

23 11 In addition, exploratory data will be collected on the following:

- 24
- 25 12
- 26
- 27 13 1. Prostate Specific Antigen (PSA) – PSA is a surrogate marker for cancer activity and is
- 28
- 29 14 measured routinely post radiotherapy. TURP typically leads to a reduction in PSA. There
- 30
- 31 15 is no known evidence on the effect of UroLift on PSA.
- 32
- 33 16 2. Time interval between proposed interventions and radiotherapy.
- 34
- 35
- 36 17
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38 18 **Patient Identification and Recruitment**

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40 20 *Sample Size:*

41 21

42 22 The sample size is 45 patients. Recruitment is expected to be completed within 12

43 23 months.

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2 *Eligibility:*

4 *Inclusion Criteria*

- 6 • Men undergoing prostate radiotherapy for prostate cancer
- 7 • Patients with moderate to severe and/or bothersome lower urinary tract symptoms
8 secondary to prostate enlargement (IPSS >8, Quality of Life score ≥ 3) and/or an
9 obstructive flow rate ($Q_{max} \leq 12$)
- 10 • Patients willing and able to provide written informed consent for the study.

11 *Exclusion Criteria*

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

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

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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.

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2 1
3
4 2 The device and system will be used in accordance with the manufacturer's instructions for use.
5
6 3

7
8 4 *Treatment Withdrawal*
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10 5
11
12 6 The Principal Investigator(PI) and research team will act in the best interest of patients at all
13
14 7 times. Therefore, the PI reserves the right to withdraw treatment at any time e.g., due to a safety
15
16 8 concern, a Significant Adverse Event (SAE), if the treatment is no longer warranted, or will cause
17
18 9 significant delay to cancer treatment.
19

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23 11 *Treatment Modification in the Event of Adverse Reaction (AR)*
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27 13 In the event of an unexpected AR, treatment may be withdrawn or modified until the event has
28
29 14 stabilised. For example, if a patient planned for UroLift has a mild allergic reaction to local
30
31 15 anaesthesia, the procedure may proceed under general anaesthesia once the AR has resolved /
32
33 16 stabilised.
34

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37 18 *PROMS Questionnaires*
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41 20 Patients will be asked to fill in PROMs questionnaires at baseline, Follow Up 1 (6 weeks post-
42
43 21 surgery) and Follow Up 2 (3 months post end of radiotherapy). Participants will be approached at
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45 22 their cancer surveillance follow up visits to fill in the research questionnaires on site on a trust
46
47 23 encrypted device. The research nurse will explain how to complete the questionnaires and answer
48
49 24 any questions. Patients will also be given the option of completing the questionnaires remotely on
50
51 25 paper or directly on REDCap within a week of administration. Paper forms returned to the office
52
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55

1 will be transcribed onto REDCap by the research nurse at the earliest available opportunity. Data
2 quality will be maintained by periodic cross-referencing by the trial manager and research team.
3

4

5 *Health economics*

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

12
13 RUtInE™ will be administered via REDCap / paper, at six months post TURP/UroLift, in line with
14 the other questionnaires in the study at Follow Up 2.

15 *Acceptability interviews*

16
17
18 In-depth interviews with a sub-sample of patients to assess acceptability of the interventions will
19 be conducted by a trained research team member.

20
21 Three patients will be interviewed at the following timepoints:

- 22
- 23 • Post randomisation
- 24 • Follow up 1 (6 weeks post intervention)
- 25 • Follow up 2 (3 months post radiotherapy)
- 26

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

3
4 Interviews will be conducted either online or face to face, according to patient preference and the
5 latest Covid-19 policy.

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

7 **Data Analysis**

8 9 *10.1 Baseline Assessments*

10
11 Baseline assessment will be performed at the time of randomisation (**Table 1**). This will include:

- 12
13 • Patient demographics
- 14 • Medical History including details of any prior prostate treatment or lower urinary tract
15 surgery
- 16 • Physical Examination
- 17 • Uroflowmetry including post void residual
- 18 • Serum PSA
- 19 • Urinalysis
- 20 • MRI scan for assessment of prostate size and anatomical suitability for intervention
21 (performed as standard of care)

22
23 The following PROMs: EPIC-50, UCLA-PCI, ICIQ-UI, EQ-5DL, CICS, PGI-I and IPSS.

1
2 1 *Surgery*

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4 2

5
6 3 Site specific standard care post-operative and discharge pathways will be followed. Surgical
7
8 4 morbidity will be recorded up to 30 days following surgery.

9
10 5

11
12 6 *Follow Up 1 (6 weeks post-surgery)*

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14 7

15
16 8 The first follow up assessment will take place at six weeks post intervention to ensure patients
17
18 9 are fit to proceed to radiotherapy. This will include

19
20
21 10

- 22
23 11 • Uroflowmetry
- 24
25 12 • Physical examination
- 26
27 13 • Serum PSA
- 28
29 14 • AE assessment
- 30
31 15 • PROMs: EPIC-50, UCLA-PCI, ICIQ-UI, EQ-5DL, CICS, PGI-I and IPSS

32
33
34 16

35
36 17 If symptoms are not yet stable enough to progress to radiotherapy, a further interval assessment
37
38 18 will take place four weeks later. Patients who fail to progress with UroLift will be reassessed and
39
40 19 offered a TURP if appropriate.

41
42 20

43
44 21 *Radiotherapy*

45
46 22

47
48 23 Details of the radiotherapy regimen and Radiotherapy Toxicity Oncology Group (RTOG) toxicity
49
50 24 data will be collected(32).

51
52
53 25

1
2 1 *Follow Up 2 (3 months post-radiotherapy)*
3

4
5 2

6 3 Subsequent assessment will take place at three months post end of radiotherapy. This will
7
8 4 include:

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10 5

- 11 6
- Uroflowmetry
 - Physical examination
 - Serum PSA
 - AE assessment
 - PROMS (as per Follow Up 1)
 - RUTInE™
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38 13 *Acceptability Interviews*

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41 15 12 In-depth interviews will be conducted in total.
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17 **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

Page 23 of 37

1
2 1 PROMS information using a unique REDCap ID. The REDCap platform adheres to a nightly back-
3
4 2 up schedule and data can be exported in the form of csv and excel files for importing into statistical
5
6 3 analysis packages.
7

8 4
9
10 5 Acceptability interviews will be recorded and transcribed with prior patient consent and stored
11
12 6 electronically on the Sponsor server.
13
14 7

15
16 8 All electronic records will be held on an encrypted password protected folder accessible on a
17
18 9 university / hospital encrypted computer on locked premises. Paper records will be kept onsite on
19
20 10 locked premises. Data will be backed up periodically onsite. Electronic and paper files will be
21
22 11 stored for five years after study completion before being deleted and securely destroyed.
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24 12

25 13 *Recording and Reporting Adverse Events*

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38 15 All Adverse Events (AE) will be recorded, graded and categorised according to Common
39
40 16 Terminology Criteria for Adverse Events (CTCAE v5.0).
41
42 17

43 18 All SAEs will be reported within 24 hours of the site team becoming aware of the event to the
44
45 19 Sponsor. All SAEs will be followed up until event resolution. It is the responsibility of the Sponsor
46
47 20 to report all Related Unexpected SAEs (RU-SAE) to REC as appropriate.
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49 21

50 22 **Patient and Public Involvement**

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23 24 Patient Reference Group (PRG)

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

9
10 The PRG will continue to advise the research team on study methodology and help to identify
11 solutions to barriers. All members are offered training and consent to the Sponsor PPI policies on
12 data protection and patient confidentiality. Meetings will be led by PPI lead (NK) and co-chaired
13 by the patient representative with an anticipation of a total of 8 meetings (6 virtual and 2 face to
14 face).

15 16 Trial Management Group (TMG)

17
18 A TMG will be appointed from the core team and meet tri-annually/as required to ensure key
19 milestones are met, discuss any safety concerns and develop potential solutions to barriers
20 identified.

21 22 Safety Review Committee (SRC)

23
24 An independent SRC will meet tri-annually and will overlook the safety and progress of the trial.
25

1 **Statistical Considerations**

3 *Sample size*

5 An estimated sample size calculation was performed based on an expected number of patients
6 who are referred to the sponsor site for radiotherapy each year. Of the 600 patients who have
7 radiotherapy each year, at least half will have symptoms associated with prostate enlargement.

8 An estimate of approximately 90 patients will be eligible for randomisation and that 50% will be
9 successfully randomised (n=45) with a 95% confidence interval of +/-10%.

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

14 *Analysis Plan*

16 *Statistical Analysis*

18 Descriptive analysis on recruitment, randomisation and retention will be conducted on Stata(35).

19 The trial will close to recruitment once the required number of patients have been recruited.

20 Descriptive analyses will include all eligible patients including reasons for patient unwillingness to
21 participate or withdrawal from study. All randomised patients will be further analysed for intended
22 outcomes.

24 *PROMS Analysis*

1
2 1 Descriptive analysis is planned for all collected PROMs data. The study has not been powered to
3
4 2 detect statistically meaningful differences in PROMs data between the two interventions.
5
6 3

7
8 4 A Delphi process will be held with our PRG to consolidate the PROMs that will be use in a larger
9
10 5 scale RCT. The group will help to define the composite endpoint of the study.
11
12 6

13 14 7 *Interview Analysis* 15 16 8

17
18 9 Thematic analysis will be used to analyse interview transcripts using the Theoretical Framework
19
20 10 of Acceptability(19). Thematic analysis of the interview transcripts may reveal aspects of the
21
22 11 intervention which require modification at an early stage and will determine whether anticipated
23
24 12 acceptability corresponds to experienced acceptability. The same three patients will be
25
26 13 interviewed as they progress through the study to capture the depth of their experience and any
27
28 14 changes in their perceptions of acceptability over time. In addition, three patients who decide to
29
30 15 end their participation in the study will be invited to interview to explore the reasons for their
31
32 16 decision. A screening log will capture reasons for patients declining to take part when approached
33
34 17 as this will provide some further indication of anticipated acceptability or lack of it.
35
36 18

37 38 39 40 19 *Health Economics Analysis* 41 42 20

43
44 21 Collection of data will enable us to assess response rates to health economics questionnaires,
45
46 22 defined as the percentage of patients returning a questionnaire at each time point out of those
47
48 23 expected (i.e. not withdrawn or died). It will also help in the development of a future trial protocol
49
50 24 for a larger trial which will include a cost-effectiveness analysis in line with NICE guidelines and
51
52 25 analysis of patients' out-of-pocket costs associated with their treatment.
53
54 26

1 Missing or spurious data

2

3
4
5
6 Data collection has been designed in accordance with NIHR carbon reduction principles to
7
8 minimise the risk of missing data. The research nurse and team will be given directed training on
9
10 completion of all data forms. All missing or spurious data will be queried with the site teams and
11
12 resolved.

13
14
15
16 Method of analysis will depend on the amount of missing data, unused or spurious in the study.
17
18 Missing data may give us insight into questionnaires / parts of questionnaires that patients don't
19
20 like or find difficult to fill out. All statistical assumptions will be reported. Sensitivity analysis will
21
22 be performed to test the uncertainty of data parameters.

23 14.4 Criteria for Early Termination of Trial

24
25
26
27 An interim review will be done at six months taking into account;

- 28 • Recruitment:

29
30
31 In the event recruitment is exceeded, early termination of the trial will be considered with
32
33 a view to early progression to a larger RCT

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

35
36
37 If the progression criteria are unlikely to be met, modifications and recommendations will
38
39 be made following further consultation with the PRG(36).

- 40 • Safety:

41
42
43 Interim analysis demonstrating intervention is harmful or a risk to the patient

- 1
2 1
3
4 2 • Any other unforeseen circumstances will be documented and reported accordingly
5
6 3

8 4 *Protocol Deviations*
9

10 5
11
12 6 Any deviations from the processes and procedures as outlined in this protocol will be documented
13
14 7 and reported to the Sponsor and regulatory bodies.
15
16 8

18 9 *Patient Confidentiality*
20
21 10

22
23 11 All investigators and trial staff will comply with the requirements of the Data Protection Act 2018
24
25 12 and in accordance with the Confidentiality Code of Practice and Data Protection Policy and
26
27 13 Procedure.
28
29 14

31 15 *Consent*
32
33 16

34
35 17 Patient consent can be obtained by a trained member of the research team. All members of the
36
37 18 research team will have up to date GCP training and adhere to GCP principles in matters related
38
39 19 to data handling.
40
41 20

42 21 **Ethics and Dissemination**
43
44 22

45
46
47
48 23 The trial has been approved by the South West Frenchay Research Ethics Committee (REC)
49
50 24 NHS Health Research Authority (HRA) and Health and Care Research Wales (HCRW). The
51
52 25 results will be published in peer-reviewed journals, presented at national meetings and
53
54 26 disseminated to patients via social media, charity and hospital websites.
55

1 Abbreviations

| | | | |
|----|----|---------|--|
| 2 | 1 | | |
| 3 | | | |
| 4 | 2 | | |
| 5 | | | |
| 6 | 3 | AE | Adverse Event |
| 7 | | | |
| 8 | 4 | AUA | American Urology Association |
| 9 | | | |
| 10 | 5 | BADS | British Association of Day Surgery |
| 11 | | | |
| 12 | 6 | BOO | Bladder Outflow Obstruction |
| 13 | | | |
| 14 | 7 | BPH | Benign Prostate Hyperplasia |
| 15 | | | |
| 16 | 8 | CICS | Couples Illness Communication Scale |
| 17 | | | |
| 18 | 9 | CI | Chief Investigator |
| 19 | | | |
| 20 | 10 | CRF | Case Report Form |
| 21 | | | |
| 22 | 11 | CTU | Clinical Trials Unit |
| 23 | | | |
| 24 | 12 | EAU | European Association of Urology |
| 25 | | | |
| 26 | 13 | EPIC-50 | Expanded Prostate cancer Index Composite –50 |
| 27 | | | |
| 28 | 14 | EQ5D | Euroqol 5D |
| 29 | | | |
| 30 | 15 | FACT-P | Functional Assessment of Cancer Therapy – Prostate |
| 31 | | | |
| 32 | 16 | GCP | Good Clinical Practice |
| 33 | | | |
| 34 | 17 | GDPR | General Data Protection Regulations |
| 35 | | | |
| 36 | 18 | GIRFT | Getting It Right First Time |
| 37 | | | |
| 38 | 19 | GP | General Practitioner |
| 39 | | | |
| 40 | 20 | ICF | Informed Consent Form |
| 41 | | | |
| 42 | 21 | ICIQ | International Consultation of Incontinence Questionnaire |
| 43 | | | |
| 44 | 22 | ICR | Institute of Cancer Research |
| 45 | | | |
| 46 | 23 | IPSS | International Prostate Symptom Score |
| 47 | | | |
| 48 | 24 | ISF | Investigator Site File |
| 49 | | | |
| 50 | 25 | LUTS | Lower Urinary Tract Symptoms |
| 51 | | | |
| 52 | 26 | MDT | Multidisciplinary Team |
| 53 | | | |
| 54 | | | |
| 55 | | | |
| 56 | | | |

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|----|----|--------|--|
| 1 | | | |
| 2 | 1 | MRI | Magnetic Resonance Imaging |
| 3 | | | |
| 4 | 2 | NHS | National Health Service |
| 5 | | | |
| 6 | 3 | NICE | National Institute for Health and Clinical Excellence |
| 7 | | | |
| 8 | 4 | NIHR | National Institute for Health Research |
| 9 | | | |
| 10 | 5 | NPCA | National Prostate Cancer Audit |
| 11 | | | |
| 12 | 6 | PGI-I | Patient Global Impression of Improvement |
| 13 | | | |
| 14 | 7 | PI | Principal Investigator |
| 15 | | | |
| 16 | 8 | PIS | Patient Information Sheet |
| 17 | | | |
| 18 | 9 | PPI | Patient and Public Involvement |
| 19 | | | |
| 20 | | | |
| 21 | 10 | PRG | Patient Reference Group |
| 22 | | | |
| 23 | 11 | PROM | Patient Related Outcome Measure |
| 24 | | | |
| 25 | 12 | PSA | Prostate Specific Antigen |
| 26 | | | |
| 27 | 13 | QOL | Quality of Life |
| 28 | | | |
| 29 | 14 | RCT | Randomised Controlled Trial |
| 30 | | | |
| 31 | 15 | REC | Research and Ethics Committee |
| 32 | | | |
| 33 | 16 | RfPB | Research for Patient Benefit |
| 34 | | | |
| 35 | 17 | R&D | Research and Development |
| 36 | | | |
| 37 | | | |
| 38 | 18 | RM | Royal Marsden |
| 39 | | | |
| 40 | 19 | RTOG | Radiation Therapy Oncology Group toxicity criteria |
| 41 | | | |
| 42 | 20 | RUTINE | Resource Utilisation Inventory for Economic Evaluation |
| 43 | | | |
| 44 | 21 | SAE | Serious Adverse Event |
| 45 | | | |
| 46 | 22 | SOP | Standard Operating Procedure |
| 47 | | | |
| 48 | 23 | TMF | Trial Master File |
| 49 | | | |
| 50 | 24 | TMG | Trial Management Group |
| 51 | | | |
| 52 | 25 | TWOC | Trial Without Catheter |
| 53 | | | |
| 54 | 26 | TURP | Transurethral Resection of Prostate |
| 55 | | | |

1
2 1 UCLA-PCI UCLA Prostate Cancer Index
3
4 2 UI Urinary incontinence
5

6 3
7

8 4 **Figure Legend**
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10 5
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12 6 **Figure 1.** Flow diagram of recruitment, randomisation and trial assessment schedule
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14 7 **Figure 2.** Stop-go Criteria for progression to full scale RCT
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For peer review only

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

1 **Declarations**

2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

2 **Declarations**

3 Ethics approval and consent to participate

4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

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

7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

8 Consent for publication

9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

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

11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

12 Availability of data and materials

13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

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

17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

18 Competing interests

19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

20 The authors declare they have no competing interests.

21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

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23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

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26 not necessarily those of the NIHR or the Department of Health and Social Care.

1
2 1
3
4 2 Authors Contributions
5
6 3
7
8 4 KW/NK/NJ/DN/DC/JS/VK/JW/MM/KG/CM/MVH/RK/CC/EY contributed to the study
9
10 5 conceptualisation, methodology, preparation, review and editing of this manuscript. There has
11
12 6 been no direct industry input into the study design or manuscript.
13
14 7 KW/NJ/NK/DN/DC/JS/JW/KG/MVH/JW/RK/CC were responsible for acquiring funding to
15
16 8 complete the proposed research. CM/MVH built the REDCap database. CM/MVH/EY/KW tested
17
18 9 the database according to Sponsor protocol.
19
20 10 KW/NK/NJ/DN/DC/JS/VK/JW/MM/KG/CM/MVH/RK/CC/EY will be involved directly in the study
21
22 11 administration, collection of data, analysis and preparation of final manuscript. All authors have
23
24 12 reviewed and approved the final submission.
25
26
27 13

28
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30
31 15

32
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34
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36
37 18 our round table discussions on establishing a stop-go criteria for a larger scale study. We are
38
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40
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46
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Figure 1 Flow diagram of recruitment, randomisation and trial assessment schedule

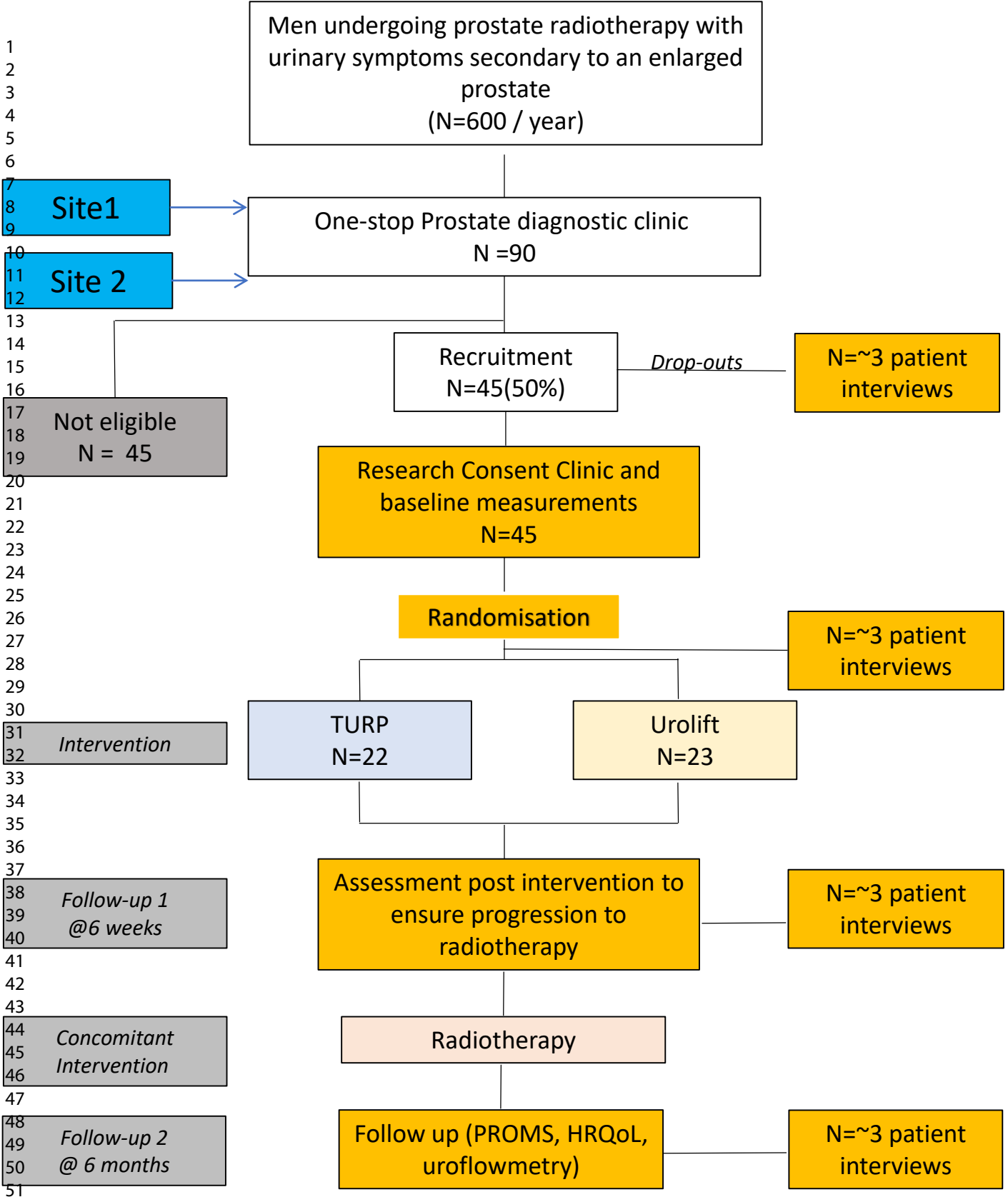


Figure 2. Stop-go Criteria for progression to full scale RCT

| 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% |



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__ |

1 **Introduction**

2

3 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 _____

4

5

6 6b Explanation for choice of comparators _____ 10 _____

7

8 Objectives 7 Specific objectives or hypotheses _____ 11-12 _____

9

10 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 _____

11

12

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14 **Methods: Participants, interventions, and outcomes**

15

16 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 _____

17

18

19 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 _____

20

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered _____ 16, 17 _____

23

24

25 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 _____

26

27

28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) _____ 17,18 _____

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30

31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____ 16 _____

32

33

34 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 _____

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40 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 _____

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 26
 2 clinical and statistical assumptions supporting any sample size calculations

4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 17,23-25

6 **Methods: Assignment of interventions (for controlled trials)**

8 Allocation:

10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any 12
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol
 13 participants or assign interventions

16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, 12
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 18 mechanism

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to 12
 21 interventions

24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome 12
 25 assessors, data analysts), and how

27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's NA
 28 allocated intervention during the trial

31 **Methods: Data collection, management, and analysis**

33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 17-23,27
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 36 Reference to where data collection forms can be found, if not in the protocol

39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be 27, 29
 40 collected for participants who discontinue or deviate from intervention protocols

| | | | | |
|----|---------------------------------|-----|---|-------------------|
| 1 | 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___ |
| 2 | | | | |
| 3 | | | | |
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| 5 | 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___ |
| 6 | | | | |
| 7 | | | | |
| 8 | | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | ___26,27___ |
| 9 | | | | |
| 10 | | 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___ |
| 11 | | | | |
| 12 | | | | |
| 13 | | | | |
| 14 | Methods: Monitoring | | | |
| 15 | | | | |
| 16 | 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___ |
| 17 | | | | |
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| 20 | | | | |
| 21 | | | | |
| 22 | | 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___ |
| 23 | | | | |
| 24 | | | | |
| 25 | 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___ |
| 26 | | | | |
| 27 | | | | |
| 28 | Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | ___25___ |
| 29 | | | | |
| 30 | | | | |
| 31 | | | | |
| 32 | Ethics and dissemination | | | |
| 33 | | | | |
| 34 | Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | ___35___ |
| 35 | | | | |
| 36 | | | | |
| 37 | 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,___ |
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|----|-------------------------------|-----|---|--------------------|
| 1 | Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | _____29_____ |
| 2 | | | | |
| 3 | | | | |
| 4 | | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____37,38_____ |
| 5 | | | | |
| 6 | | | | |
| 7 | 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_____ |
| 8 | | | | |
| 9 | | | | |
| 10 | Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | _____35,36_____ |
| 11 | | | | |
| 12 | | | | |
| 13 | 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_____ |
| 14 | | | | |
| 15 | | | | |
| 16 | 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_____ |
| 17 | | | | |
| 18 | | | | |
| 19 | | | | |
| 20 | 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_____ |
| 21 | | | | |
| 22 | | | | |
| 23 | | | | |
| 24 | | 31b | Authorship eligibility guidelines and any intended use of professional writers | _____36_____ |
| 25 | | | | |
| 26 | | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | _____NA_____ |
| 27 | | | | |
| 28 | | | | |
| 29 | Appendices | | | |
| 30 | | | | |
| 31 | Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | _____37,38_____ |
| 32 | | | | |
| 33 | | | | |
| 34 | 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_____ |
| 35 | | | | |
| 36 | | | | |

*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”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.



A [study protocol for a](#) randomised feasibility study **CO**mparing Urolift and **St**andard
Transurethral resection of prostate **A**head of **R**adiotherapy in men with urinary
symptoms secondary to prostate enlargement [in Southwest London and North Cumbria](#)

COSTAR

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| 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:

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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:

1 The Sponsor has responsibility for the legal aspects of the trial, helping to support delivery and
2 provide independent review of the safety and clinical aspects of the trial. The Sponsor is
3 responsible for hosting the trial database.
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10 Funded by the National Institute of Health Research, Research for Patient Benefit grant (NIHR
11 203152)
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16 ~~Word Count: 3998~~
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18 **Abstract**

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23 **Introduction**

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

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44 A multi-centre, two-arm study designed in collaboration with a Patient Reference Group to assess
45 the feasibility of randomising men with prostate cancer and co-existing urinary symptoms due to
46 prostate enlargement to TURP or UroLift ahead of radiotherapy.
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52 45 patients will be enrolled and randomised (1:1) using a computer-generated programme to
53 TURP or UroLift.
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2 1
3
4 2 Recruitment and retention will be assessed over a 12-month period. Information on clinical
5
6 3 outcomes, Adverse Events, and costs will be collected. Clinical outcomes and Patient Reported
7
8 4 Outcome Measures (PROMs) will be measured at baseline, six-weeks post-intervention and three
9
10 5 months following radiotherapy. A further 12 in-depth interviews will be conducted with a subset of
11
12 6 patients to assess acceptability using the Theoretical Framework of Acceptability.
13
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17 8 Descriptive analysis on all outcomes will be performed using Stata (StataCorp 2021).
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19 9

20 21 10 **Ethics and Dissemination**

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23 11
24
25 12 The trial has been approved by the Research Ethics Committee (REC) ~~and NHS~~ Health Research
26
27 13 Authority (HRA) and Health and Care Research Wales (HCRW). The results will be published in
28
29 14 peer-reviewed journals, presented at national meetings and disseminated to patients via social
30
31 15 media, charity and hospital websites.
32
33 16

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35
36 17 **Trial registration IRAS 280225 Clinicaltrials.gov NCT05840549**
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38 18

39 40 19 **Keywords**

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42 20
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44 21 Urolift, transurethral resection of prostate, prostate radiotherapy, prostate cancer, urinary
45
46 22 symptoms, bladder outlet obstruction
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48 23

49 50 24 **Strengths and Limitations**

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55 26
 - This study is designed in partnership with patients

- 1
- 2 1 • Randomisation of patients to the two treatment arms avoids selection bias
- 3
- 4 2 • A mixed methods approach allows for maximisation of data collection
- 5
- 6 3 • As this is an open label interventional study, it is not possible to blind patients or
- 7
- 8 4 surgeons to the treatment assigned to patients therefore potentially introducing bias
- 9
- 10 5 • This study is a pilot study aimed at assessing feasibility of randomisation and is
- 11
- 12 6 therefore not powered to detect differences in treatment outcomes
- 13
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1 Background

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6 Approximately 14,000 men undergo radical radiotherapy for prostate cancer in England every
7
8 year, over 85% of men are over 60 years of age and half will have lower urinary tract symptoms
9
10 (LUTS) secondary to prostatic enlargement(1, 2).

11
12
13
14 The short-term complications of untreated bladder outlet obstruction from prostatic enlargement
15
16 in the context of prostate radiotherapy, although rare, can be disastrous, resulting in urinary
17
18 retention, sepsis and renal failure. In the long-term, urinary symptoms can continue to worsen
19
20 compounded by the effects of radiotherapy. Transurethral Resection of Prostate (TURP) is the
21
22 mainstay surgical intervention for outlet obstruction due to prostate enlargement prior to
23
24 radiotherapy. Studies reporting functional outcomes in patients undergoing TURP and
25
26 radiotherapy are limited(3, 4). TURP and radiotherapy can both cause incontinence independently
27
28 and the available evidence suggests a risk of incontinence as high as 27% patients who undergo
29
30 both(5). When patients have TURP to treat prostate enlargement after radiotherapy, case studies
31
32 suggests the risk of incontinence and other complications (e.g. strictures) are higher than TURP
33
34 before radiotherapy(5). Therefore, for radiotherapy to safely go ahead, outlet obstruction should
35
36 first be addressed.
37
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41

42 UroLift(NeoTract Inc., Pleasanton, CA USA) is a newer, minimally invasive alternative to TURP,
43
44 approved by the National Institute of Health and Care Excellence (NICE)(6). A growing body of
45
46 evidence including three meta-analyses supports its use in benign disease(7-9).
47
48
49

50 There are two randomised control trials (RCTs) for benign disease. The LIFT study conducted in
51
52 19 centres across the USA, Canada and Australia designed to evaluate the safety and
53
54 effectiveness of UroLift in men with Benign Prostate Hyperplasia (BPH) compared to sham. At 12
55

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

7
8 UroLift has not been formally tested in patients undergoing prostate radiotherapy with coexisting
9 urinary tract symptoms. A subgroup analysis performed on retrospective data suggested that
10 patients who had previously undergone prostate radiotherapy experienced symptom relief without
11 an increase in adverse events(12). Extrapolating from the findings of reduced morbidity and
12 recovery time in benign trials, it is likely UroLift could reduce potential treatment delay due to
13 recovery from surgery. Furthermore, the UroLift system could potentially be used as a surrogate
14 for fiducial markers, potentially introducing an efficiency saving(13, 14).

15
16 If UroLift is shown to be comparable to TURP for men undergoing radiotherapy, the findings could
17 have an impact on patient choice of treatment, quality of life during and beyond their cancer
18 treatment. UroLift, unlike TURP, can be performed under local anaesthetic and is therefore safer.
19 UroLift has been shown to provide quicker symptom resolution and return to normal activity.
20 Patients can go home on the same day and avoid the need for a catheter afterwards over 70% of
21 the time(11). With healthcare systems still overburdened by the aftermath of Covid-19, a shorter,
22 simpler procedure has attractions for patients, healthcare providers and funders. These benefits
23 need to be balanced against the long-term durability of the procedure.

24
25 Data from a NICE-commissioned external assessment centre suggest savings of up to £1,267
26 per patient with UroLift compared to TURP in benign disease(6). Based on internal estimated

1
2 1 audit figures(15), at least 4,200 patients undergo TURP annually, leading to potential National
3
4 2 Health Service (NHS) savings of over £5.3 million per year with UroLift.
5
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8 4 *Description of treatments*
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10 5
11
12 6 Both TURP and UroLift are well established interventions and widely used for treatment of the
13
14 7 enlarged prostate in benign disease with medium to long-term clinical outcome data available(11,
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16 8 16-18).
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21 10 TURP is an operation which can be performed under general or regional anaesthetic. A
22
23 11 cystoscope is passed into the urethra meatus, along the length of the urethra to the prostate. The
24
25 12 obstructing prostate lobes are resected using mono polar or bipolar energy to create a channel
26
27 13 for improved urinary flow. Haemostasis is achieved by coagulation followed by insertion of a
28
29 14 catheter for irrigation post procedure. Typically, patients stay for 1-2 nights post-operatively and
30
31 15 the catheter remains for a variable period.
32
33 16

34
35 17 UroLift can be performed under local anaesthetic, sedation or general anaesthetic. The system
36
37 18 comprises of two single-use components, a delivery device and an implant. The implant is made
38
39 19 of a nitinol capsular tab, a polyethylene terephthalate monofilament and a stainless-steel end-
40
41 20 piece. A modified cystoscope is passed into the urethral meatus, along the length of the urethra
42
43 21 to the prostate. The delivery device deploys the implants into the prostate to 'pin' back the lobes
44
45 22 of the prostate to create a channel, improving flow. Typically, 2-4 implants are used per patient.
46
47 23 In the benign setting, nine out of ten patients do not require a catheter following UroLift.
48
49 24

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51
52 25 *Research Governance*
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54 26

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

4 5 **Aim**

6
7 The aim is to assess the feasibility of randomising patients in a randomised controlled trial
8 comparing TURP and UroLift and to define the important outcomes to patients that should be
9 used to define treatment success. The results will shape the design of a larger trial that will
10 compare the clinical and cost-effectiveness of the two interventions.

11 12 **Hypothesis**

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

17 18 **Objectives**

19 20 *Primary Objectives*

- 21
22 1. Recruitment - To evaluate whether it is possible to recruit patients to an RCT comparing
23 standard treatment with a new treatment untested in men with prostate cancer.
- 24 2. Retention – To assess the proportion of patients who will complete the trial protocol

- 1
2 1
3
4 2 *Secondary Objectives*
5
6 3
7
8 4 1. Assess safety and efficacy of UroLift and TURP
9
10 5 2. Determination of patient acceptability of the proposed interventions and Patient Related
11
12 6 Outcome Measures (PROMs)
13
14
15 7 3. Information on costs of the two interventions
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21 9 **Study Design**

22
23
24 10
25
26 11 This trial has been designed with Patient and Public Involvement (PPI). This is a prospective,
27
28 12 multi-centre, two-arm, randomised controlled trial. Patients will be recruited from two
29
30 13 geographically diverse regions (Southwest London and North Cumbria). Randomisation will be
31
32 14 provided by a computer-generated program at the Institute of Cancer Research (ICR) on a 1:1
33
34 15 basis to TURP or UroLift (**Figure 1**).
35
36 16

37
38
39 17 The randomisation is not blinded; participant and research team will know which treatment
40
41 18 pathway has been allocated to the patient.
42
43 19
44
45

46 20 **End Points**

47 48 21 49 22 *Primary Endpoints*

50
51
52
53 23
54
55 24 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

- 1
- 2 1 4. Safety – 30-day surgical morbidity rates will be collected with respect to but not limited to
- 3
- 4 2 infection, urinary retention, and bleeding.
- 5
- 6 3
- 7
- 8 4 5. Efficacy of procedure – Improvement in baseline IPSS score and Uroflowmetry
- 9
- 10 5 (measured by maximum flow rate and post void urine residual).
- 11
- 12 6
- 13
- 14 7 6. Cost of the two interventions.
- 15
- 16 8
- 17
- 18 9 7. Re-operation rate for technical failure to reduce outflow obstruction.
- 19
- 20
- 21 10
- 22

23 11 In addition, exploratory data will be collected on the following:

- 24
- 25 12
- 26
- 27 13 1. Prostate Specific Antigen (PSA) – PSA is a surrogate marker for cancer activity and is
- 28
- 29 14 measured routinely post radiotherapy. TURP typically leads to a reduction in PSA. There
- 30
- 31 15 is no known evidence on the effect of UroLift on PSA.
- 32
- 33 16 2. Time interval between proposed interventions and radiotherapy.
- 34
- 35 17
- 36
- 37

38 18 **Patient Identification and Recruitment**

39 19

40 20 *Sample Size:*

41 21

42 22 The sample size is 45 patients. Recruitment is expected to be completed within 12

43 23 months.

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2 *Eligibility:*

4 *Inclusion Criteria*

- 6 • Men undergoing prostate radiotherapy for prostate cancer
- 7 • Patients with moderate to severe and/or bothersome lower urinary tract symptoms
8 secondary to prostate enlargement (IPSS >8, Quality of Life score ≥ 3) and/or an
9 obstructive flow rate ($Q_{max} \leq 12$)
- 10 • Patients willing and able to provide written informed consent for the study.

11 *Exclusion Criteria*

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

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

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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.

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2 1
3
4 2 The device and system will be used in accordance with the manufacturer's instructions for use.
5
6 3
7

8 4 *Treatment Withdrawal*
9

10 5
11
12 6 The Principal Investigator(PI) and research team will act in the best interest of patients at all
13
14 7 times. Therefore, the PI reserves the right to withdraw treatment at any time e.g., due to a safety
15
16 8 concern, a Significant Adverse Event (SAE), if the treatment is no longer warranted, or will cause
17
18 9 significant delay to cancer treatment.
19

20
21 10
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23 11 *Treatment Modification in the Event of Adverse Reaction (AR)*
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25 12
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27 13 In the event of an unexpected AR, treatment may be withdrawn or modified until the event has
28
29 14 stabilised. For example, if a patient planned for UroLift has a mild allergic reaction to local
30
31 15 anaesthesia, the procedure may proceed under general anaesthesia once the AR has resolved /
32
33 16 stabilised.
34

35 17
36
37 18 *PROMS Questionnaires*
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42 20 Patients will be asked to fill in PROMs questionnaires at baseline, Follow Up 1 (6 weeks post-
43
44 21 surgery) and Follow Up 2 (3 months post end of radiotherapy). Participants will be approached at
45
46 22 their cancer surveillance follow up visits to fill in the research questionnaires on site on a trust
47
48 23 encrypted device. The research nurse will explain how to complete the questionnaires and answer
49
50 24 any questions. Patients will also be given the option of completing the questionnaires remotely on
51
52 25 paper or directly on REDCap within a week of administration. Paper forms returned to the office
53
54
55

1 will be transcribed onto REDCap by the research nurse at the earliest available opportunity. Data
2 quality will be maintained by periodic cross-referencing by the trial manager and research team.
3

4

5 *Health economics*

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

12
13 RUtInE™ will be administered via REDCap / paper, at six months post TURP/UroLift, in line with
14 the other questionnaires in the study at Follow Up 2.

15 *Acceptability interviews*

16
17
18 In-depth interviews with a sub-sample of patients to assess acceptability of the interventions will
19 be conducted by a trained research team member.

20
21 Three patients will be interviewed at the following timepoints:

- 22
- 23 • Post randomisation
- 24 • Follow up 1 (6 weeks post intervention)
- 25 • Follow up 2 (3 months post radiotherapy)
- 26

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

3
4 Interviews will be conducted either online or face to face, according to patient preference and the
5 latest Covid-19 policy.

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

7 **Data Analysis**

9 *10.1 Baseline Assessments*

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

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

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

1
2 1 *Surgery*
3

4 2

5
6 3 Site specific standard care post-operative and discharge pathways will be followed. Surgical
7
8 4 morbidity will be recorded up to 30 days following surgery.
9

10 5

11
12 6 *Follow Up 1 (6 weeks post-surgery)*
13

14 7

15
16 8 The first follow up assessment will take place at six weeks post intervention to ensure patients
17
18 9 are fit to proceed to radiotherapy. This will include
19

20
21 10

22
23 11 • Uroflowmetry

24
25 12 • Physical examination

26
27 13 • Serum PSA

28
29 14 • AE assessment

30
31 15 • PROMs: EPIC-50, UCLA-PCI, ICIQ-UI, EQ-5DL, CICS, PGI-I and IPSS
32
33

34 16

35
36 17 If symptoms are not yet stable enough to progress to radiotherapy, a further interval assessment
37
38 18 will take place four weeks later. Patients who fail to progress with UroLift will be reassessed and
39
40 19 offered a TURP if appropriate.
41

42 20

43
44 21 *Radiotherapy*
45

46 22

47
48 23 Details of the radiotherapy regimen and Radiotherapy Toxicity Oncology Group (RTOG) toxicity
49
50 24 data will be collected(32).
51

52
53 25
54
55
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1
2 1 *Follow Up 2 (3 months post-radiotherapy)*

3
4 2

5
6 3 Subsequent assessment will take place at three months post end of radiotherapy. This will
7
8 4 include:

9
10 5

- 11
12 6
- Uroflowmetry
 - Physical examination
 - Serum PSA
 - AE assessment
 - PROMS (as per Follow Up 1)
 - RUTInE™
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36 13 *Acceptability Interviews*

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39 15 12 In-depth interviews will be conducted in total.

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17 **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

Page 23 of 41

1
2 1 PROMS information using a unique REDCap ID. The REDCap platform adheres to a nightly back-
3
4 2 up schedule and data can be exported in the form of csv and excel files for importing into statistical
5
6 3 analysis packages.
7

8 4
9
10 5 Acceptability interviews will be recorded and transcribed with prior patient consent and stored
11
12 6 electronically on the Sponsor server.
13
14 7

15
16 8 All electronic records will be held on an encrypted password protected folder accessible on a
17
18 9 university / hospital encrypted computer on locked premises. Paper records will be kept onsite on
19
20 10 locked premises. Data will be backed up periodically onsite. Electronic and paper files will be
21
22 11 stored for five years after study completion before being deleted and securely destroyed.
23
24 12

25 13 *Recording and Reporting Adverse Events*

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32 15 All Adverse Events (AE) will be recorded, graded and categorised according to Common
33
34 16 Terminology Criteria for Adverse Events (CTCAE v5.0).
35
36 17

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38 18 All SAEs will be reported within 24 hours of the site team becoming aware of the event to the
39
40 19 Sponsor. All SAEs will be followed up until event resolution. It is the responsibility of the Sponsor
41
42 20 to report all Related Unexpected SAEs (RU-SAE) to REC as appropriate.
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44 21

45 22 **Patient and Public Involvement**

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52 24 Patient Reference Group (PRG)

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

9
10 The PRG will continue to advise the research team on study methodology and help to identify
11 solutions to barriers. All members are offered training and consent to the Sponsor PPI policies on
12 data protection and patient confidentiality. Meetings will be led by PPI lead (NK) and co-chaired
13 by the patient representative with an anticipation of a total of 8 meetings (6 virtual and 2 face to
14 face).

15 16 Trial Management Group (TMG)

17
18 A TMG will be appointed from the core team and meet tri-annually/as required to ensure key
19 milestones are met, discuss any safety concerns and develop potential solutions to barriers
20 identified.

21 22 Safety Review Committee (SRC)

23
24 An independent SRC will meet tri-annually and will overlook the safety and progress of the trial.
25

1 **Statistical Considerations**

3 *Sample size*

5 An estimated sample size calculation was performed based on an expected number of patients
6 who are referred to the sponsor site for radiotherapy each year. Of the 600 patients who have
7 radiotherapy each year, at least half will have symptoms associated with prostate enlargement.

8 An estimate of approximately 90 patients will be eligible for randomisation and that 50% will be
9 successfully randomised (n=45) with a 95% confidence interval of +/-10%.

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

14 *Analysis Plan*

16 *Statistical Analysis*

18 Descriptive analysis on recruitment, randomisation and retention will be conducted on Stata(35).

19 The trial will close to recruitment once the required number of patients have been recruited.

20 Descriptive analyses will include all eligible patients including reasons for patient unwillingness to
21 participate or withdrawal from study. All randomised patients will be further analysed for intended
22 outcomes.

24 *PROMS Analysis*

1
2 1 Descriptive analysis is planned for all collected PROMs data. The study has not been powered to
3
4 2 detect statistically meaningful differences in PROMs data between the two interventions.
5
6 3

7
8 4 A Delphi process will be held with our PRG to consolidate the PROMs that will be use in a larger
9
10 5 scale RCT. The group will help to define the composite endpoint of the study.
11
12 6

13 7 *Interview Analysis*

14 8
15
16 9 Thematic analysis will be used to analyse interview transcripts using the Theoretical Framework
17
18 10 of Acceptability(19). Thematic analysis of the interview transcripts may reveal aspects of the
19
20 11 intervention which require modification at an early stage and will determine whether anticipated
21
22 12 acceptability corresponds to experienced acceptability. The same three patients will be
23
24 13 interviewed as they progress through the study to capture the depth of their experience and any
25
26 14 changes in their perceptions of acceptability over time. In addition, three patients who decide to
27
28 15 end their participation in the study will be invited to interview to explore the reasons for their
29
30 16 decision. A screening log will capture reasons for patients declining to take part when approached
31
32 17 as this will provide some further indication of anticipated acceptability or lack of it.
33
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40 19 *Health Economics Analysis*

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42
43 21 Collection of data will enable us to assess response rates to health economics questionnaires,
44
45 22 defined as the percentage of patients returning a questionnaire at each time point out of those
46
47 23 expected (i.e. not withdrawn or died). It will also help in the development of a future trial protocol
48
49 24 for a larger trial which will include a cost-effectiveness analysis in line with NICE guidelines and
50
51 25 analysis of patients' out-of-pocket costs associated with their treatment.
52
53 26
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55
56

1 Missing or spurious data

2

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

7

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

12

13 14.4 Criteria for Early Termination of Trial

14

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

16

- 17 • Recruitment:

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

20

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

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

24

- 25 • Safety:

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

- 1
2 1
3
4 2 • Any other unforeseen circumstances will be documented and reported accordingly
5
6 3

8 4 *Protocol Deviations*
9

10 5
11
12 6 Any deviations from the processes and procedures as outlined in this protocol will be documented
13
14 7 and reported to the Sponsor and regulatory bodies.
15
16 8

18 9 *Patient Confidentiality*
20
21 10

22
23 11 All investigators and trial staff will comply with the requirements of the Data Protection Act 2018
24
25 12 and in accordance with the Confidentiality Code of Practice and Data Protection Policy and
26
27 13 Procedure.
28
29 14

31 15 *Consent*
32
33 16

35 17 Patient consent can be obtained by a trained member of the research team. All members of the
36
37 18 research team will have up to date GCP training and adhere to GCP principles in matters related
38
39 19 to data handling.
40
41 20

44 21 **Ethics and Dissemination**
45
46 22 –

48 23 The trial has been approved by the Research Ethics Committee (REC) NHS Health Research
49
50 24 Authority (HRA) and Health and Care Research Wales (HCRW). The results will be published in
51
52 25 peer-reviewed journals, presented at national meetings and disseminated to patients via social
53
54 26 media, charity and hospital websites.
55

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.

1
2 1 ~~A two-stage round table discussion involving the core team and a patient representative was held~~
3
4 2 ~~to determine the stop-go criteria for proceeding to a larger multicentre RCT applying a Nominal~~
5
6 3 ~~Group Technique(36) (Figure 2).~~
7

8 4
9
10 5 ~~At the end of the study, the team hope to understand whether such a trial is acceptable to all~~
11
12 6 ~~stakeholders, is methodologically robust and feasible. Key findings of this study will be published~~
13
14 7 ~~in peer-reviewed journals, presented at national meetings and disseminated to patients via social~~
15
16 8 ~~media, charity and trust websites. The findings of this study will add new evidence to current~~
17
18 9 ~~limited literature on this subject and help men in the future to make informed decisions about their~~
19
20 10 ~~prostate cancer treatment options.~~
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1 Abbreviations

| | | | |
|----|----|---------|--|
| 2 | 1 | | |
| 3 | | | |
| 4 | 2 | | |
| 5 | | | |
| 6 | 3 | AE | Adverse Event |
| 7 | | | |
| 8 | 4 | AUA | American Urology Association |
| 9 | | | |
| 10 | 5 | BADS | British Association of Day Surgery |
| 11 | | | |
| 12 | 6 | BOO | Bladder Outflow Obstruction |
| 13 | | | |
| 14 | 7 | BPH | Benign Prostate Hyperplasia |
| 15 | | | |
| 16 | 8 | CICS | Couples Illness Communication Scale |
| 17 | | | |
| 18 | 9 | CI | Chief Investigator |
| 19 | | | |
| 20 | 10 | CRF | Case Report Form |
| 21 | | | |
| 22 | 11 | CTU | Clinical Trials Unit |
| 23 | | | |
| 24 | 12 | EAU | European Association of Urology |
| 25 | | | |
| 26 | 13 | EPIC-50 | Expanded Prostate cancer Index Composite –50 |
| 27 | | | |
| 28 | 14 | EQ5D | Euroqol 5D |
| 29 | | | |
| 30 | 15 | FACT-P | Functional Assessment of Cancer Therapy – Prostate |
| 31 | | | |
| 32 | 16 | GCP | Good Clinical Practice |
| 33 | | | |
| 34 | 17 | GDPR | General Data Protection Regulations |
| 35 | | | |
| 36 | 18 | GIRFT | Getting It Right First Time |
| 37 | | | |
| 38 | 19 | GP | General Practitioner |
| 39 | | | |
| 40 | 20 | ICF | Informed Consent Form |
| 41 | | | |
| 42 | 21 | ICIQ | International Consultation of Incontinence Questionnaire |
| 43 | | | |
| 44 | 22 | ICR | Institute of Cancer Research |
| 45 | | | |
| 46 | 23 | IPSS | International Prostate Symptom Score |
| 47 | | | |
| 48 | 24 | ISF | Investigator Site File |
| 49 | | | |
| 50 | 25 | LUTS | Lower Urinary Tract Symptoms |
| 51 | | | |
| 52 | 26 | MDT | Multidisciplinary Team |
| 53 | | | |
| 54 | | | |
| 55 | | | |
| 56 | | | |

| | | | |
|----|----|--------|--|
| 1 | | | |
| 2 | 1 | MRI | Magnetic Resonance Imaging |
| 3 | | | |
| 4 | 2 | NHS | National Health Service |
| 5 | | | |
| 6 | 3 | NICE | National Institute for Health and Clinical Excellence |
| 7 | | | |
| 8 | 4 | NIHR | National Institute for Health Research |
| 9 | | | |
| 10 | 5 | NPCA | National Prostate Cancer Audit |
| 11 | | | |
| 12 | 6 | PGI-I | Patient Global Impression of Improvement |
| 13 | | | |
| 14 | 7 | PI | Principal Investigator |
| 15 | | | |
| 16 | 8 | PIS | Patient Information Sheet |
| 17 | | | |
| 18 | 9 | PPI | Patient and Public Involvement |
| 19 | | | |
| 20 | | | |
| 21 | 10 | PRG | Patient Reference Group |
| 22 | | | |
| 23 | 11 | PROM | Patient Related Outcome Measure |
| 24 | | | |
| 25 | 12 | PSA | Prostate Specific Antigen |
| 26 | | | |
| 27 | 13 | QOL | Quality of Life |
| 28 | | | |
| 29 | 14 | RCT | Randomised Controlled Trial |
| 30 | | | |
| 31 | 15 | REC | Research and Ethics Committee |
| 32 | | | |
| 33 | 16 | RfPB | Research for Patient Benefit |
| 34 | | | |
| 35 | 17 | R&D | Research and Development |
| 36 | | | |
| 37 | | | |
| 38 | 18 | RM | Royal Marsden |
| 39 | | | |
| 40 | 19 | RTOG | Radiation Therapy Oncology Group toxicity criteria |
| 41 | | | |
| 42 | 20 | RUTINE | Resource Utilisation Inventory for Economic Evaluation |
| 43 | | | |
| 44 | 21 | SAE | Serious Adverse Event |
| 45 | | | |
| 46 | 22 | SOP | Standard Operating Procedure |
| 47 | | | |
| 48 | 23 | TMF | Trial Master File |
| 49 | | | |
| 50 | 24 | TMG | Trial Management Group |
| 51 | | | |
| 52 | 25 | TWOC | Trial Without Catheter |
| 53 | | | |
| 54 | 26 | TURP | Transurethral Resection of Prostate |
| 55 | | | |

| | | | |
|---|---|----------|----------------------------|
| 1 | | | |
| 2 | 1 | UCLA-PCI | UCLA Prostate Cancer Index |
| 3 | | | |
| 4 | 2 | UI | Urinary incontinence |
| 5 | | | |

8 4 **Figure Legend**

12 6 **Figure 1.** Flow diagram of recruitment, randomisation and trial assessment schedule

14 7 **Figure 2.** Stop-go Criteria for progression to full scale RCT

For peer review only

1 **Declarations**

3 Ethics approval and consent to participate

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

8 Consent for publication

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

12 Availability of data and materials

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

18 Competing interests

20 The authors declare they have no competing interests.

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2 1
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4 2 Authors Contributions
5
6 3
7
8 4 KW/NK/NJ/DN/DC/JS/VK/JW/MM/KG/CM/MVH/RK/CC/EY contributed to the study
9
10 5 conceptualisation, methodology, preparation, review and editing of this manuscript. There has
11
12 6 been no direct industry input into the study design or manuscript.
13
14 7 KW/NJ/NK/DN/DC/JS/JW/KG/MVH/JW/RK/CC were responsible for acquiring funding to
15
16 8 complete the proposed research. CM/MVH built the REDCap database. CM/MVH/EY/KW tested
17
18 9 the database according to Sponsor protocol.
19
20 10 KW/NK/NJ/DN/DC/JS/VK/JW/MM/KG/CM/MVH/RK/CC/EY will be involved directly in the study
21
22 11 administration, collection of data, analysis and preparation of final manuscript. All authors have
23
24 12 reviewed and approved the final submission.
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26
27 13

28
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31 15

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Appendix 1 – Trial Consent Form

CONSENT FORM

CO-STAR

A randomised feasibility study **CO**mparing Urolift and **Standard** Transurethral 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. | | |

1

2

3 _____

4 Name of Participant _____ Date _____ Signature _____

5

6

7 _____

8 Name of Person taking consent _____ Date _____ Signature _____

9

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