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| **Full Title:** | A randomised controlled trial of minimally invasive surgical treatments for bladder outlet obstruction due to enlarged prostate in the National Health Service |
| **Short Title/Acronym:** | Prostate Resection versus Minimally Invasive Surgery Evaluation Trial (**PREMISE Trial**) |
| **Protocol Version Number & Date:** | V6.0 24 Sep 2024 |

Statement:

This protocol has regard for the HRA guidance.

# RESEARCH REFERENCE NUMBERS

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| **IRAS Number:** | 318198 |
| **NHS REC Reference:** | 23/NW/0053 |
| **ISRCTN:** | 50571778 |
| **Protocol Authors:** | Tobias Page, Marcus Drake, Faye Wolstenhulme, Naomi McGregor, Ruth Latter, Emma Clark, Cristina Fernandez Garcia, Laura Ternent, Alaa Abouhajar, Julia Phillipson, Adam Milne, Marzieh Shahmandi, Helen Mossop, James Wason and Jennifer Wilkinson |

# RESEARCH SPONSOR

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| **Sponsor Name:** | The Newcastle upon Tyne Hospitals NHS Foundation Trust |
| **Sponsor Reference:** | 10092 |

# RESEARCH FUNDER(S)

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| **Funder:** | This study/project is funded by the NIHR HTA programme (131984). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. |

# SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the Research Governance Framework, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures and other regulatory requirements as applicable.

The undersigned agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

**Representative of the Research Sponsor**

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**Position:**

**Signature:** **Date:**

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**Signature:** **Date:**

**Senior Statistician**

**Name:** Helen Mossop

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**Newcastle Clinical Trials Unit Representative**

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**Signature:** **Date:**

# PROTOCOL ACCEPTANCE SIGNATURE PAGE

**Short Trial Title: PREMISE Trial**

**Principal Investigator**

I have carefully read and understood protocol version 6.0. I agree to conduct the trial in compliance with Good Clinical Practice.

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| | Data Monitoring Committee (DMC) Chair<br>Prof. Graeme MacLennan, Director, The Centre for Healthcare Randomised Trials (CHaRT), University of Aberdeen |

# TRIAL SUMMARY

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| **Trial Title** | A randomised controlled trial of minimally invasive surgical treatments for bladder outlet obstruction due to enlarged prostate in the National Health Service. |
| **Acronym** | **PREMISE Trial**<br>Prostate Resection versus Minimally Invasive Surgery Evaluation Trial |
| **Summary of Trial Design** | Multi-arm, multi-centre, non-inferiority personalised randomised controlled trial, with six-month internal pilot, to determine the clinical and cost-effectiveness of three minimally invasive treatments (MITS) compared to transurethral resection of prostate (TURP) for treatment of bladder outlet obstruction (BOO) due to enlarged prostate. |
| **Summary of Participant Population** | Men aged 50 years or older with prostate volume ≥30 ml to ≤ 80ml, who are offered surgery for bladder outlet obstruction (BOO) within an NHS setting. |
| **Intervention** | Prostatic urethral lift (PUL), Temporary Implantable Nitinol Device (iTIND), Water vapour ablation (Rezum) and TURP (Control). Patients can be randomised only among treatments they are willing to receive. |
| **Planned Sample Size** | Minimum of 536 |
| **Planned Number of Sites** | 10* |
| **Intervention Duration** | Single procedure treatment |
| **Follow Up Duration** | Three years |
| **Planned Trial Period** | 71 months |

*If recruitment to the trial is lower than anticipated, consideration will be made to the addition of further research sites.

# Contents

# GLOSSARY OF ABREVIATIONS

| ABBREVIATION | DEFINITION |
|---|---|
| AE | Adverse Event |
| BOO | Bladder Outlet Obstruction |
| BPE | Benign Prostate Enlargement |
| CACE | Complier Average Casual Effect |
| CBA | Cost benefit analysis |
| CEA | Cost-Effectiveness Acceptability |
| CEAC | Cost-Effectiveness Acceptability Curves |
| CI | Chief Investigator |
| CNS | Central Nervous System |
| CRF | Case Report Form |
| CUA | Cost Utility Analysis |
| CV | Contingent Valuation |
| DCE | Discrete Choice Experiment |
| DMC | Data Monitoring Committee |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| HTA | Health Technology Assessment |
| ICF | Informed Consent Form |
| ICU | Intensive Care Unit |
| ICIQ-MLUTS | International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms |
| ICIQ-MLUTSsex | International Consultation on Incontinence Questionnaire Male Sexual Matters Associated with Lower Urinary Tract Symptoms |
| ICIQ-LUTSqol | International Consultation on Incontinence Questionnaire Lower Urinary Tract Symptoms Quality of Life |
| IMD | Indices of Multiple Deprivation |
| I-PSS | International Prostate Symptom Score |
| I-PSS-QOL | International Prostate Symptom Score Quality of Life |
| IPW | Inverse Probability Weighting |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trials Number |

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|---|---|
| iTIND | Temporary Implantable Nitinol Device |
| ITT | Intention-to-treat |
| IV | Instrumental Variable |
| LCRN | Local Clinical Research Network |
| MCID | Minimally Clinically Important Difference |
| MITS | Minimally Invasive Treatment |
| NCTU | Newcastle Clinical Trials Unit |
| NHS | National Health Service |
| NI | Non-inferiority |
| PI | Principal Investigator |
| PIC | Participant Identification Centre |
| PIS | Participant Information Sheet |
| PROM | Patient Reported Outcome Measure |
| PUL | Prostatic Urethral Lift |
| QA | Quality Assurance |
| QC | Quality Control |
| R&D | Research & Development |
| RCT | Randomised Control Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOP | Standard Operating Procedure |
| SUR | Seemingly Unrelated Regression |
| TMG | Trial Management Group |
| TMF | Trial Master File |
| TSC | Trials Steering Committee |
| TURP | Transurethral Resection of Prostate |
| URSE | Unexpected Related Serious Event |
| USM | Urgent Safety Measure |

# 1. BACKGROUND

The prostate gland encircles the urethra at the bladder outlet and is important for sexual function, notably in the process of synthesis of ejaculatory fluid. With age, the gland enlarges in response to the male sexual hormones, causing the central part of the gland to encroach into the urethra. Consequently, blockage and distortion mean that the flow of the urinary stream becomes obstructed. Thus, benign prostate enlargement (BPE) with ageing causes increasing bladder outlet obstruction (BOO), a situation known as benign prostatic obstruction (BPO). BPO is a major contributor to the emergence of lower urinary tract symptoms (LUTS). Voiding symptoms (e.g. slow stream, intermittency, hesitancy, straining, dribbling) and post voiding symptoms (e.g. post-micturition dribble) reflect problems occurring when passing urine or immediately after. Many men also experience storage symptoms (e.g. increased daytime urinary frequency, nocturia, urgency, incontinence). The most severe situation as BOO progresses is acute urinary retention, when a man becomes unable to pass urine at all, leading to painful bladder distension which requires emergency treatment with an indwelling catheter (IDC) to relieve the physical blockage until definitive treatment can be undertaken.

44,000 new cases of symptomatic benign prostatic obstruction (BPO) are diagnosed each year [10] and 90% of men aged 50 to 80 years suffer from at least one LUTS, which can affect quality of life, occupation and other activities [3]. Since BPO is a disease of older men, the number of patients affected is likely to increase significantly by the year 2025, in line with population ageing. Disease-specific HRQOL measures are significantly worse in men with higher symptom frequency and severity ratings in population-based studies.

While many men are managed successfully with conservative and pharmaceutical interventions, a substantial proportion do not gain sufficient symptom improvement. Where voiding LUTS are a significant contributor to an individual's symptoms, they may then be recommended to undergo interventional therapy to reduce BOO. 25,000 [10] surgical procedures to relieve BPO are currently performed each year in the NHS; approximately 60% of these are for men who are voiding but have symptoms. These procedures work by treating the part of the prostate which is impinging on the bladder outlet and urethra. Transurethral resection of the prostate (TURP) is a surgical procedure using electrocautery to remove the intrusive part of the gland under endoscopic visual control. This has been the main approach to managing voiding LUTS for many years, with a high chance of improving LUTS, and is a widespread and standardised procedure. Adaptations such as transurethral resection in saline (TURIS) have been introduced, and laser technology options are now also used as an alternative to TURP, working with a different energy source to remove the intrusive tissue [11].
These interventions are effective, but require a hospital stay (median stay of two days) and carry risk of surgical complications (notably blood transfusion, infection, urethral stricture, and anaesthetic problems). Reported peri-operative mortality is up to 0.25% [12]. An indwelling catheter is necessary for a varying amount of time after these interventions. Time off work is usually a month and full recovery may take up to three months. Importantly, TURP is known to carry long-term adverse effects, notably incontinence due to damage of the urinary sphincter or its nerve supply. Late complications (urethral stricture and bladder neck contracture) are reported in up to 9.8% [11,12,46] of procedures. Impaired sexual function is also a substantial problem for many (70%) patients considering this surgery. It is caused by three factors:

- Reduced ejaculate volume, due to loss of the prostate ducts
- Retrograde ejaculation (dry orgasm) caused by dividing the bladder neck, a structure which normally closes during semen emission to prevent the ejaculate from being able to enter the bladder
- Erectile dysfunction, the mechanism of which is not entirely clear, but may involve damage of fine nerve endings by the energy source.

The above issues have led to development of alternatives with shorter recovery time, and less impact on both sexual function and continence. Innovations have focused on varying the physical method to relieve the partial BOO or enhancing the precision of BPE tissue removal to preserve key anatomical structures. This trial proposes to evaluate three more recent innovations in comparison to TURP:

1. Prostatic urethral lift (PUL), which uses a physical method to retract the intrusive tissue by anchoring it and compressing it against the prostate pseudo-capsule outer layer. This might reduce risk of sexual function impairment, as selective placement of the anchoring points enables preservation of the prostatic ducts and bladder neck, while use of energy sources that could affect nerve endings is avoided. [3,2]
2. Rezum, which is a computer-controlled system for directing steam into tissue planes for removal of obstructing prostatic tissue. This is potentially quicker and easier than conventional resection, and might preserve the bladder neck, hence avoiding retrograde ejaculation.[2]
3. Temporary Implantable Nitinol Device (iTIND), which is a metal implant that is inserted into the prostatic cavity and left in place for five to seven days before being removed. It makes three radial channels into the prostate and bladder neck, increasing the space through which urine flows and can be inserted with patients awake with mild sedation.[6]

# 2. RATIONALE

Many of the newer minimally invasive treatments (MITS) appear to preserve sexual function [3,7], at least in the short term, but the perception is that they are not achieving the same extent of voiding improvements obtained with more complete removal of the prostate tissue in TURP. [8] Each of the MITS can be completed with fewer requirements for general or regional anaesthesia, and so it may be possible to treat some men who would otherwise be considered unsuitable for intervention due to the risk of anaesthesia. In general, quicker recovery and return to normal activity is also expected. NICE guidance on management of LUTS in men (CG97) [9], was last updated prior to the mainstream introduction of these methods into clinical practice and makes no reference to their evaluation or recommendations regarding their use. This trial will be critical in informing any such upcoming evaluation by NICE and other guideline writers and policymakers.

A significant advantage of MITS is that they can be delivered in an outpatient setting without the need for a general anaesthetic which may reduce patient and staff risk. Additionally, these MITS avoid the need for in-patient stay, decreasing patients' exposure to time in hospital, bringing efficient use of resources and reducing risks of acquiring hospital infections, such as COVID-19. As a consequence of decreased service delivery in the NHS due to COVID-19 restrictions, and the likely longer-term changes

in service configuration, MITS are a highly attractive area to allow the backlog of general anaesthetic cases waiting for TURP to be treated promptly, as long as these MITS are shown to be efficacious and safe.

For 100 procedures, the specific equipment and consumable costs of TURP are approximately £29,000. [53] Significant risks may be associated with TURP, additional NHS costs resulting from delayed discharge from hospital, re-admissions and increased primary care utilisation. These unwanted consequences will increase in the future, as surgery for BPO increases in line with the ageing male population and because most operations are conducted on older men (in 2010-11, 41% of TURP operations were for men of 75 years or more in age). Thus, reduction in the number of surgical procedures and widespread adoption of MITS offers direct cost savings, reduced resource use, and supports the possibility of reconfigurations of surgical services.

**Rezum Water Vapour Therapy:** This system consists of a portable radiofrequency (RF) generator and delivery device that is introduced via the urethra (transurethral approach) and guided by direct visualization through a telescopic lens placed within the delivery device. RF energy from the generator is applied to an inductive coil in the delivery device to heat up a controlled amount of water, converting the water into vapour or steam. The thermal energy created outside the body is delivered into the prostate tissue through a tiny needle with emitter holes to ablate the targeted obstructive prostate tissue. The endoscopic part of the procedure takes less than 10 minutes and can be done in a day surgery setting. With each nine second delivery of steam, a predictable volume of tissue is ablated. Rezum works via convective heating (rather than conductive), with the water vapour confined to its delivery site, and can be done under local anaesthesia (usually with sedation). After the procedure it is necessary to leave a catheter in place for a few days (usually three to seven); this is necessary as there is no tissue removal or compression immediately following the procedure, and so time is required to allow swelling to ease. Water vapour is usually injected into the transition zone (TZ) tissue but can also target the central zone (CZ), allowing treatment of glands with median lobe enlargement. MRI studies done to assess changes in the TZ demonstrated that by six months post treatment, the average volume reduction was 38%. There have also been several case series published in the urological literature evidencing the clinical benefit of this technique [15,20]. Level one evidence comes from the PIVOTAL II study, which was an RCT showing significant improvements in I-PSS, quality of life and flow rate,[15] maintained for three years, along with preservation of sexual function. Surgical retreatment rate was 4.4% (4-year data), and no late-onset related adverse events, or de novo erectile dysfunction, were reported. The US FDA approved this intervention in 2015. Several other studies found similar reductions in LUTS and preserved sexual function at one to two years. [21,22] Early UK results were reported at the BAUS meeting in 2018, and a larger cohort was presented at major urological meetings in 2019.[23] In August 2018, NICE released a Medtech Innovation briefing (IPG 625) [2] which provided costings for practitioners and hospitals. The potential benefits of adopting Rezum, as reported to the adoption team are day case procedure, reduces costs and risks of cancellation. A quick procedure resulting in more cases completed in one session, and sexual function and continence is generally preserved as the procedure avoids the use of an implant.

**Prostatic urethral lift:** PUL is a minimally invasive treatment which does not excise or ablate tissue, and so avoids some adverse effects. PUL is also known as Urolift (trade name). PUL is intended for men with bothersome LUTS, where intervention is being considered, but TURP or equivalent is not

felt acceptable by the patient. Nearly all other less invasive procedures have involved a mechanism of action using thermal energy to effect tissue necrosis. Because tissue ablation relies on subsequent healing, recovery is often not achieved for several weeks, during which time substantial symptoms may be present. Some thermal ablation technologies are associated with sexual dysfunction (erectile dysfunction ≤3%, ejaculatory dysfunction 5%-15%).[24] PUL was developed to avoid delivery of energy. It was approved by the FDA in 2013, and by NICE in 2015. PUL involves placing non-absorbable sutures with a nitinol prostate capsular anchor and a stainless-steel urethral end piece to mechanically open up the anterior prostatic fossa and disobstruct the urethra.[25] Treatment can be administered in an outpatient setting under local anaesthesia. [26] Patient recovery is quick, with mild to moderate adverse events that typically resolve by two to four weeks.[27] Need for further treatment is relatively low (2.5-9%). [27,28] Patients with enlarged median lobes may also be treated with similar outcomes.[29] Recent data has also supported the use of PUL as a treatment for catheterised men. Despite the limited evidence base, PUL has become a widely disseminated treatment option for patients with LUTS worldwide.[28]

**Temporary Implantable Nitinol Device (iTIND):** Second generation Temporary Implantable nitinol device (iTIND) (medi-Tate Ltd, Israel) is a crimped prostatic device that exerts a radial force within the prostate over a number of days before being removed. It opens the prostatic cavity and bladder neck via reshaping of the prostatic cavity by ischaemic necrosis.[6] It is inserted under sedation, local or general anaesthetic, left for five to seven days and then removed. Manufacturer's two year follow up data have been published, showing I-PSS improvement from 20.5 to 8.5 at 24 months and similar adverse events to other MITS. However, this was a single arm trial funded by the manufacturer. One prospective multicentre study [6] has been published and, as yet no randomised control trial. The one-year data was reported on 67 men and 51 at two years. Prostate volume was in the range of 16-65 mls. Quality of life scores at two years had improved from 4.0 to 1.8, based on the I-PSS quality of life question. The flow rate was shown to increase from 7.6 to 16 ml/s at two years. Men undergoing the procedure under sedation demonstrated moderate to low pain scores on a visual analogue scale of 3.2 +/- 1.6. No Clavien-Dindo complications >2 were demonstrated and the retention rate seen was approximately 10%. Retreatment rates of 6.2% have been demonstrated within a limited two year period and overall failure of the treatment to improve symptoms was seen in 14.8% at two years with evidence that failure was more common in men with median lobe prostate enlargement. [30,31] NICE guidance IPG641 [32] reports limited evidence on safety and efficacy and the requirement of further research. EAU guidelines do not recommend treatment with iTIND, due to a lack of evidence base. Given this calls recommendation to consider and explore the failure of innovative new treatments we are keen to include iTIND as one of the investigatory arms.

**Rationale for selection of technologies to be investigated:** Much of the available data on MITS is of limited scope and is of limited quality. It does not constitute a reliable evidence base on which to make clear recommendations to individual patients or for health services. A comparative trial with TURP, the widely accepted standard treatment and most common modality will provide robust data for guideline writers and policy makers in the future. The techniques have been introduced with some clinical research evidence for their use in treating LUTS. Much of the initial evidence was from commercially led studies used to meet regulatory device requirements [13,14,15]. There remains a relative lack of comparative evidence from rigorous randomised controlled trials (RCTs) to demonstrate which treatments have the optimal balance between side-effects and effectiveness in

which groups of men. For PUL, a review identified two studies [16]. The L.I.F.T study claimed that PUL can provide rapid and durable relief of LUTS without compromising sexual function. The BPH6 trial compared PUL with TURP, indicating greater improvement of LUTS with TURP, while PUL achieved better quality of recovery, ejaculatory function, and quality of sleep. In its summary of evidence for 2019, the EAU Guidelines panel for Male LUTS stated that PUL improves I-PSS, flow rate and QoL with a low incidence of sexual side effects, but the improvements are inferior to TURP at 24 months. One review identified five studies reporting the outcomes of Rezum, where symptoms reduced by 46-60% and maximum flow rate ($Q_{max}$) improved by 44-72%.[17]. For iTIND, the majority of studies published have been retrospective in nature and commercially sponsored; the two prospective clinical trials had important limitations. [6,14] The PREMISE study will thus fill an existing evidence gap that needs addressing to inform treatment for this important group.

Patient and public involvement

The trial design was developed with input from patient representatives with direct experience of LUTS. They recognised the importance of the trial, highlighting concerns around "uncertainty of treatment choice and side effects" and "need for future treatments" as a result. They pointed out that based on these concerns potential randomisation to the "TURP" arm would not be a major barrier to participation, as there is good data supporting efficacy and longevity. The access to multiple new MITS and three year duration was seen as a positive. The groups guidance was followed on randomisation (e.g. would participants be willing to accept the treatments on offer in a randomisation of 1:1:1:1)and the range of treatments being offered and the clinical equipoise in what treatments to offer. The acceptability of different modes of delivery such as local anaesthetic and/or sedation, the statistical significance was discussed and in particular the PPI felt that the need for clearer understanding of which patients would benefit most from minimally invasive treatments was important.

### 2.1. Risk Assessment

This trial is categorized as:

Type A: no higher than that of standard medical care

# 3. OBJECTIVES AND OUTCOME MEASURES

| | **Objectives** | **Outcome Measures** |
|---|---|---|
| **Primary** | To compare the clinical effectiveness of 3 minimally invasive treatments (MITS) to transurethral resection of prostate (TURP) for treatment of bladder outlet obstruction (BOO) due to enlarged prostate over 12 months | Change in international prostate symptom score (I-PSS) from baseline to 12 months post-intervention |

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|---|---|---|
| **Primary Economic** | To compare the cost effectiveness of 3 minimally invasive treatments (MITS) to transurethral resection of prostate (TURP) for treatment of bladder outlet obstruction (BOO) due to enlarged prostate | Incremental cost per quality-adjusted life year (QALY) gained at 12 months post-intervention<br>Cost-effectiveness acceptability curves (CEACs) to assess the probability of each of the interventions being considered cost-effective at different willingness-to-pay (WTP) thresholds for a gained QALY<br>QALYs will be calculated using responses to the EQ-5D-5L questionnaire |
| **Secondary** | To compare impact on bladder voiding efficiency (BVE) and maximum flow rate (Qmax) | Change from baseline to 12 months post-intervention in:<br>• Post void residual<br>• Maximum flow rate (Qmax) |
| | To compare incidence of adverse events | Adverse events up to six months post-intervention collected via:<br>• Operative parameters<br>• Adverse event review at six weeks and six months post-intervention |
| | To compare impact on incontinence | International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms Module (ICIQ-MLUTS) at baseline, six months, 12 months, two and three years post-intervention |
| | To compare impact on sexual function | ICIQ-MLUTSsex at baseline, six months, 12 months, two and three years post-intervention |
| | To compare impact on quality of life and general health | • I-PSS-QOL at baseline, six months, 12 months, two and three years post-intervention<br>• ICIQ-LUTSqol at baseline, six months, 12 months, two and three years post-intervention<br>• EQ-5D-5L at baseline, six weeks post-intervention, six months, 12 months, two and three months post-intervention |
| | To establish the most suitable outcome measure for the context of male LUTS intervention | Correlation of I-PSS / ICIQ-MLUTS |

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| | To assess the impact of urinary and sexual symptoms on quality of life | Correlation of overall QOL (ICIQ-LUTSqol) with symptom scores from ICIQ-MLUTSsex and I-PSS questionnaires |
| | To compare the amount of time spent in hospital post-intervention | Length of post-intervention hospital stay |
| | To compare the use of and duration of catheterisation perioperatively and post-intervention | Perioperative and post-intervention catheterisation duration and subsequent use of catheters up to three years post-intervention |
| | To compare the hospital attendance rate post-intervention | Number and rate of hospital attendances (in patient or outpatient visits) for events/conditions possibly associated with BPE, condition progression, intervention, (including routine follow-up appointments post-intervention) or treatment failure up to 12 months post-intervention |
| | To compare the blood transfusion rate post-intervention | Number of patients requiring blood transfusions up to six weeks post-intervention |
| | To compare the incidence of acute urinary retention post-intervention | Number of patients experiencing post-intervention acute urinary retention up to 12 months post-intervention |
| | To compare the surgical re-intervention rate | Number of patients requiring surgical re-intervention of any type for their urinary symptoms up to 3 years post-intervention |
| **Secondary Economic** | To estimate and compare costs and quality of life following intervention over 12 months | Average healthcare costs per participant over 12 months post-intervention for each area of resource use<br><br>Utility scores derived from responses to the EQ-5D-5L questionnaire at baseline, six weeks post-intervention, six months and 12 months post-intervention<br><br>Average QALYs per participant at 12 months post-intervention |

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| | To compare the cost effectiveness of the interventions at two years and three years post-intervention | Incremental cost per quality-adjusted life year (QALY) gained at two and three years post-intervention<br>Cost- effectiveness acceptability curves to assess the probability of each of the interventions being considered cost-effective at different WTP thresholds for a gained QALY at two and three years post-intervention |
| | To model costs and quality of life over a patient's lifetime | Average healthcare costs per participant over their lifetime |
| | To model the incremental cost per QALY over the patient's lifetime | ICERs and CEACs derived by extrapolating costs and QALYs from the data observed during the trial |
| | To estimate the net benefit value of the interventions for each individual | Participants' willingness to pay for each intervention or combination of interventions<br>Incremental net benefit of interventions |
| **Exploratory** | To assess carbon footprint of each intervention and its associated pathway | An assessment of the carbon cost of each intervention |

# 4. TRIAL DESIGN

Multi-arm, multi-centre, open-label, non-inferiority, personalised randomised controlled trial with a six-month internal pilot with defined progression criteria. In total, a minimum of 536 participants will be recruited and followed up for three years post-intervention.

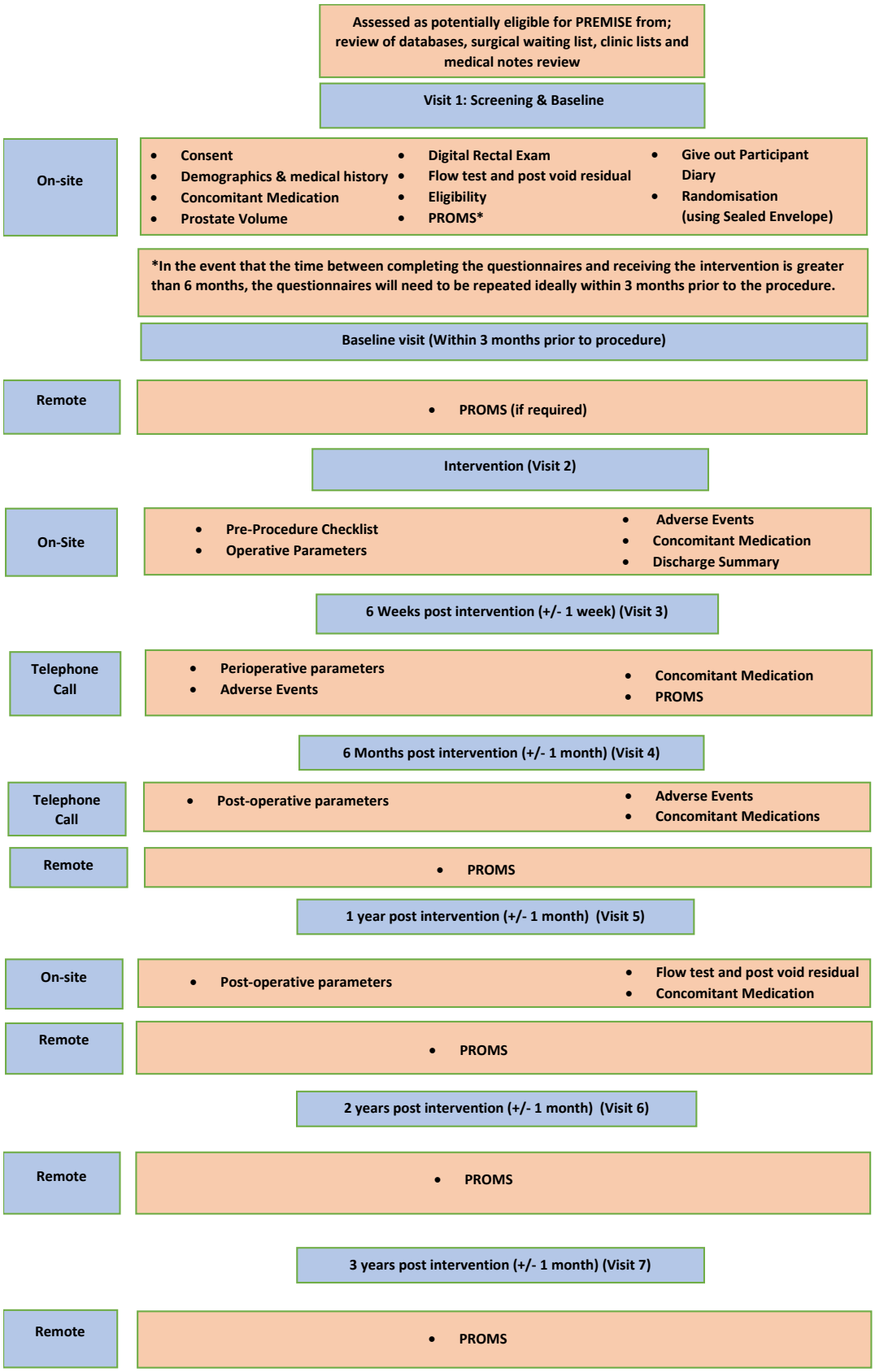
Patients who are willing to receive at least two of the four trial interventions can be randomised among treatments they are willing to receive. There are 11 possible randomisation schemes for patients to choose from. (See section 7.2.) Site staff will be counselled to retain equipoise between all four interventions and should not aim to influence the participants choice for the interventions they are willing to receive. To mitigate against surgeon influence the pattern of participant choice will be monitored across sites.

All sites will offer all interventions. In some sites this may be through the use of a Hub and Spoke model, which functions by allowing patients to access a variety of treatments within their locality but not necessarily in their originating hospital or trust. Where this is the case trial participants may receive their study intervention at another hospital or trust, referred to as a 'Spoke' site. The 'Hub' site will be responsible for organising and conducting all study visits, (apart from the study

intervention as detailed above), collecting all study data, communicating with trial participants and liaising with the site/trust carrying out the study intervention as required.

By the nature of the different delivery of treatments and the need to record treatment-specific operative parameters and resource use, blinding of the participant, surgeon, clinical team, Health Economics and TMG is not possible.

## 4.1. Study flow diagram



# 5. STUDY SETTING

Patients will be recruited and treated in NHS secondary care centres and will also complete remote follow-up. Staff groups involved in the recruitment and delivery of the trial will vary by the existing pathway of the recruiting hospital, currently there is much heterogeneity in how these services are delivered across the country, with some being delivered completely at a consultant level as a one stop clinic, others utilizing nurse specialists. Other centres continue with a more traditional clinic model. Participants will also be identified through local neighbouring trusts acting as participant identification centres (PICs). After recruitment, treatment will be delivered by a surgeon who has demonstrated proficiency in the technique to a defined manufacturers standard to avoid the impact of any perceived learning curve (see section 8.1.).

# 6. ELIGIBILITY CRITERIA

## 6.1. Inclusion Criteria

1. Men aged 50 years or over
2. Prostate volume of between 30ml ($cm^3$) and up to and including 80ml ($cm^3$) (measured by ultrasound or cross-sectional scan) (please refer to section 7.1.3 where a patient has previously had 2 or more volume assessments by different measurements within the 12 months prior to consent)
3. Eligible for surgery for presumed BOO within an NHS setting
4. Willing and able to comply with trial procedures, visit schedules, trial restrictions and requirements
5. Willing and able to provide informed consent

## 6.2. Exclusion criteria

1. Any known or suspected prostate cancer treated or untreated; (If PSA has been performed outside of trial investigations PSA density ≥0.15 would be an exclusion unless prostate cancer has been excluded) (See section 7.5.3)
2. Known or suspected neuropathic bladder dysfunction
3. Any previous minimally invasive or surgical treatment to the prostate or bladder outlet
4. Contraindication for both spinal and general anaesthesia
5. Catheterised or catheter dependent self catheterising patients
6. Predicted life expectancy less than three years
7. Active participation in another interventional urological trial where the ongoing intervention may impact the outcomes of this trial (See 'Co-enrolment' in section 6.3.)

**NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver. Protocol waivers are not permitted**.

### 6.3. Co-enrolment

Co-enrolment of PREMISE participants to other current trials will be checked and agreed with the Chief Investigator to avoid undesirable treatment interactions or effects on PREMISE outcomes and/or safety concerns.

# 7. TRIAL PROCEDURES

## 7.1. Recruitment

### 7.1.1. Patient Identification

Potential participants within secondary care will be identified and approached about the study. Where dedicated LUTS clinics already exist, men who have reached a point of deciding on whether to proceed to surgical intervention will be approached about the trial. Where dedicated LUTS clinics are not established, men will be approached about participation in general urology clinics within secondary care when the treating clinician discusses failure of medical management and the option for surgical intervention. Potential participants may be identified through database searches by their direct care team e.g. those currently waiting for standard of care surgical intervention.

Each research site lead will publicise the study within their own trust and ensure that colleagues (medical and nursing) who may receive referrals of LUTS patients are aware of the study and able to identify potential participants. Each site will aim to ensure that all eligible patients are informed of the trial via the screening of clinic lists and surgical schedules and posters will be available for waiting rooms.

Potentially eligible patients will be identified and approached by a member of their direct care team. This will usually be in person at a clinic appointment, but may also be in the form of a phone call, with the PIS then being emailed or posted out to the patient. Patients who express an interest in the study to their direct care team and who agree to be contacted by the research team, will then be approached by a member of the research team to discuss the trial and be invited to attend a trial screening visit delivered by the research team. A patient recruitment video and patient experience videos will also be provided via the trial website, to provide layered provision of patient information and increase trial accessibility.

For potential participants identified at PIC sites, who have received a PIS and verbally consented to be contacted by the research team, the PIC site will notify the trial site. Upon notification, a member of the research team will contact the potential participant to further discuss the trial and invite to a screening visit.

Sites can utilise the trial poster to inform potential participants of the trial and advise to discuss potential participation with their local direct care team during routine clinical visits.

The screening log will be completed for all patients invited to participate, including those who decline to participate or who consent to participate but are subsequently found to be ineligible. This will include the collection of data including age, ethnicity and where provided, reasons for decline or ineligibility will be documented.

Patients referred for the trial who decline participation, or who are found to be ineligible will be sent a letter to their treating consultant and GP stating that there will be no further involvement from the research team and that the patient's care is being handed back to follow the standard of care pathway.

### 7.1.2. Consent

Potentially eligible participants will be invited for a research specific screening visit where informed consent will be taken. Potential participants will have sufficient time to review the trial documentation prior to this screening visit this will likely be 24 hours but may be less depending on patient driven requests and circumstances, e.g. the patient living a distance away from the hospital and not wishing to return for a separate visit to consent to the study. Patients will be encouraged to ask questions about the trial and consider whether they wish to participate. Patients should be willing to have at least two of the four possible procedures.

The patient will be informed of their right to withdraw from the trial at any time without being subject to any resulting detriment, by revoking his informed consent. Consent discussions will be documented in the participant's medical records.

Written informed consent for the trial will be taken by a delegated member of the research team, (in agreement with local site policies) who is appropriately trained and delegated to do so. All consenting staff will be required to complete the study specific training which will include a section on trial consent and the importance of delivering information about the various study arms with equipoise, in order to avoid inadvertently biasing potential patients. Consent will be obtained prior to any activities undertaken as part of the screening visit (Visit 1).

The original signed consent form will be retained in the Investigator Site File (ISF), with a copy provided to the patient and a copy filed or scanned into the patient's medical notes (depending on local hospital records/patient notes). Participants will specifically consent to their GP and care team (and referring PIC where applicable), being informed of their participation in the trial and for long term follow up by notes review.

In the case of protocol amendments or information becoming available which may affect the participant's willingness to continue in the trial, it may be necessary to re-consent the participant on an updated consent form (after necessary approvals are obtained).

### 7.1.3. Screening, Randomisation Choice and Eligibility Assessment

Following consent participants will be asked which of the randomisation arms they would be willing to be randomised between (see section 7.2.1.). Randomisation arm choice should be documented in the participant medical records. Participants will be able to change their mind about their randomisation choice up until the point of randomisation.

Prior to entry into the trial, all patients will be screened to assess eligibility, ensuring compliance with the trial inclusion and exclusion criteria (see section 6.).

The following assessments will be performed in order to assess eligibility:

- Demographics and medical history including medication history
- Prostate volume (see section 7.5.2.)
- Digital Rectal Exam to exclude cancer (see section 7.5.3.)
- An eligibility checklist will be completed and a copy filed in the patient's medical notes. Only medically qualified personnel formally delegated by the PI to assess eligibility may confirm eligibility.

The patient will be informed whether they meet eligibility criteria for the trial and randomisation performed. Patients who do not meet the eligibility criteria will continue with their standard treatment pathway. These patients will not take part in the trial and no further data will be collected. These patients will be recorded on the screening database with reasons for non-eligibility documented.

## 7.2. Randomisation

### 7.2.1. Randomisation scheme

There will be 11 randomisation schemes available (six 1:1 options, four 1:1:1 options and one 1:1:1:1 option:

1. Prostatic urethral lift (PUL) vs Rezum vs Temporary Implantable Nitinol Device (iTIND) vs TURP
2. TURP vs Rezum vs PUL
3. TURP vs PUL vs iTIND
4. TURP vs Rezum vs iTIND
5. PUL vs iTIND vs Rezum
6. TURP vs Rezum
7. TURP vs PUL
8. TURP vs iTIND
9. Rezum vs PUL
10. Rezum vs iTIND
11. PUL vs iTIND

For each scheme, randomisation will be performed using permuted random blocks of variable length.

### 7.2.2. Randomising a participant

Once consent is obtained and eligibility confirmed, the research team should reaffirm with the participant the trial treatment options they are willing to be randomised between and document this in the participant medical notes.

The research team should then access the randomisation system and select the trial treatments the participant is willing to receive. The randomisation system will then allocate the patient to receive one of the selected procedures.

The treatment allocation should be documented in the participant medical records and the patient should be informed of their randomised treatment.

Randomisation will be performed by delegated and trained members of the research team using the Sealed Envelope system. This is a central, secure, 24-hour web-based randomisation system. Local research staff delegated the randomisation task on the delegation log will be provided by the NCTU team with a unique login and password for the randomisation system.

| Randomisation system web address:<br>https://www.sealedenvelope.com/access/<br>The system is available 24 hours a day, 7 days a week |
|---|

In the event that the online randomisation system is not accessible, the site team should contact the NCTU Database Management Team in normal working hours (9am – 5pm Monday to Friday, excluding bank holidays and Newcastle University closures):
E-mail: nctu.database.support@newcastle.ac.uk
NCTU can liaise with Sealed Envelope support to investigate the cause.

## 7.3. Post-Intervention Participant Diary

In order to facilitate the collection of post-intervention hospital attendance rate and catheterisation data, all participants will be given a participant diary at the screening visit. They will be encouraged to use this to record:

- Any hospital attendances (in patient or outpatient visits) from the time of intervention up to 12 months post-intervention for events/conditions possibly associated with:
  - BPE
  - Condition progression
  - Intervention, (including routine follow-up appointments post-intervention)
  - Treatment failure
- Any episodes of catheterisation from the point of their surgical intervention up to their three years post-intervention visit
- Details of any surgical re-intervention required for urological symptoms up to their three years post-intervention visit

Participants will be asked to refer back to this diary at each visit.

## 7.4. Participant Pathway

Following randomisation patients will need to wait (as per standard NHS waiting lists) to have their intervention. The waiting times may vary for different interventions and could be up to a year for TURP. Trial staff will ensure administration of the allocated treatment and participants will undergo the planned treatment within their local site hospital or spoke site. Participants will undergo post-procedural follow-up as per standard care, with a discharge letter being sent to the designated lead research team within the participant's local site hospital or hub site (as applicable) once the patient is discharged from hospital following their surgical intervention. The local lead research team will co-ordinate the six week and six month telephone calls, the 12 months visit and the administration and data entry of patient reported outcome measure (PROM)s (where these are to be completed on paper) at these visits. The administration (and data entry where required) of the PROMs at the two and three year follow up visits and sending of gift vouchers following completion of these questionnaires may be performed by either the local research team or centrally by the NCTU team, where patients require paper questionnaires/vouchers to be sent. Consent will be sought to collect and securely hold participant names and contact details for these purposes. Follow-up timepoints will be measured from the date of intervention, (or in cases where the intervention does not take place, measured from the planned date). Participation will end and participants will resume standard clinical pathways three years from time of intervention. Depending on the date of their intervention some participants may only be followed up for two years.

## 7.5. Trial Assessments

### 7.5.1. Demographics and Medical History

At the screening visit, demographics and medical history will be collected, to include:

- Date of birth
- Postcode (to allow derivation of IMD)
- History of medical conditions outlined in eligibility criteria incl. diabetes, VTE, bleeding disorders, ischemic heart disease and neurological disorders
- Urological surgical interventions (previous and planned)
- Height and weight
- Current medications and non-drug therapy (incl. anti-platelet and anticoagulant drugs)
- Previous medication for LUTS
- Current participation in other intervention trials

### 7.5.2. Prostate Volume

Where prostate volume has not been measured as standard of care prior to consent, this will be measured at the screening visit by a transrectal ultrasound by a delegated member of the trial team or a radiographer. Where an existing cross-sectional scan relevant to the current episode of urinary symptoms is available within 12 months of the date of informed consent, this would be acceptable to use for volume assessment. Where a patient has previously had 2 or more volume assessments by different measurements within the 12 months set period prior to consent (particularly which suggest

conflicting results), the clinician should use their discretion as to the most appropriate modality to use (as per local clinical practice) and justification must be documented within the patient's medical records. Any concerns about eligibility can be discussed with the CI.

### 7.5.3. Digital Rectal Exam

Where cancer has not previously been excluded by either DRE, or MRI, or a negative biopsy within 12 months prior to consent, a Digital Rectal Exam will be performed at the screening visit by a delegated member of the trial team in order to exclude cancer.

### 7.5.4. Flow Test and Post Void Residual

**Uroflowmetry:** Uroflowmetry is the measurement of voided urine (in millilitres) per unit of time (in seconds). The important elements of the test are voided volume (which should be >125 mL for a valid test), maximum flow rate (Qmax), and the curve of the flow (which should be bell shaped). In men, a Qmax >15 mL/s is considered normal, whereas a Qmax <10 mL/s is considered abnormal. Use of any type of calibrated flowmeter is acceptable for this trial.

**Post-void residual:** post-void residual volume (PVR) is the amount of urine retained in the bladder after a voluntary void and functions as a diagnostic tool. Both conventional ultrasound or a dedicated ultrasound bladder scanner can be used to assess the post-void residual. For this trial either ultrasound technique is acceptable and catheter assessment should not be used.

Measurement of post-void residual should ideally be within 10 minutes of voiding, for accurate measurement.

Where a flow test and post-void residual has not been performed as standard care within six months prior to consent, or where a test has been performed within six months but resulted in a voided volume <125ml, this test can either be completed at the end of the screening visit once eligibility has been confirmed or at a separate visit before the procedure within six weeks of screening. If the participant is unable to produce a voided volume of >125 ml they may still be eligible for the trial.

### 7.5.5. Participant Reported Outcome Measures

There are a number of Patient Reported Outcome Measures (PROMs) in the form of trial participant questionnaires, which can be completed on paper or using the trial ePRO system (electronic Patient-Reported Outcomes). Participants will be sent a link to the Questionnaire by email. Participants will use this link to complete the questionnaire on their smart phone, computer, laptop or other electronic device. Where questionnaires are completed on paper, these will be accompanied with a pre-paid envelope to be returned to the lead site research team for entry into the trial database.
Where participants have requested to complete questionnaires on paper, sites will be encouraged to send these out to participants in advance of their six weeks, six months, one, two and three years post-intervention visits, in order to maximise data return within the allowed visit windows.

The majority of questionnaires will be in English, however, questionnaires EQ-5D-5L and I-PSS with I-PSS QOL are also available in several validated languages. Site staff to enquire with the NCTU trial management team.

The PROMs are required at screening, six weeks, six months, 12 months and two and three years post-intervention. In the event that the time between completing the screening questionnaires and receiving the intervention is greater than 6 months, the questionnaires will need to be repeated within three months prior to the procedure.

#### 7.5.5.1. I-PSS and I-PSS QOL

The International Prostate Symptom Score (I-PSS) [48] is a patient reported outcome measure scored on the answers to seven questions concerning urinary symptoms. There is also a single best answer question concerning quality of life, known as the I-PSS-QOL. The I-PSS and I-PSS-QOL are accepted as the official worldwide symptoms assessment tool for male patients with lower urinary symptoms.

The I-PSS component questions for urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of that particular symptom. These are scored from 0 to 5, with 5 being most symptomatic. The total score is a range from 0 to 35 (asymptomatic to very symptomatic). The symptoms assessed per question are: (1) Incomplete emptying, (2) Frequency, (3) Intermittency, (4) Urgency, (5) Weak Stream, (6) Straining and (7) Nocturia.

The I-PSS-QOL single question to assess quality of life has answers that range from “delighted” to “terrible” and scored from 0 to 6.

#### 7.5.5.2. ICIQ-MLUTS

The ICIQ-MLUTS is a questionnaire for evaluating male lower urinary tract symptoms and impact on quality of life (QoL) in research and clinical practice across the world. The ICIQ-MLUTS is derived from the fully validated ICSmaleSF questionnaire. [49]

The questionnaire is composed of 13 sections with each section asking about:

- Severity of a particular symptom on a scale of 0 to 4, with (4) being most symptomatic.
- How much the patient is bothered by each particular symptom on a scale of 0 to 10, with (0) being ‘not at all’ and (10) being ‘a great deal’.

#### 7.5.5.3. ICIQ-MLUTSsex

The ICIQ-MLUTSsex is a patient-completed questionnaire for detailed evaluation of male sexual matters associated with their lower urinary tract symptoms and impact on quality of life (QoL) in research and clinical practice across the world. The ICIQ-MLUTSsex is derived from the fully validated ICSmale questionnaire and provides robust measure to assess the impact of sexual matters on outcome. [50]

The questionnaire is composed of four sections with each section asking about:

- The grading of a particular sexual matter/impact on the patient's sex life, on a scale of 0 to 3, with (3) being most severe/most problematic.
- How much of a problem each issue is for the patient, on a scale of 0 to 10, with (0) being 'not a problem' and (10) being 'a serious problem'.

#### 7.5.5.4. ICIQ-LUTSqol

The ICIQ-LUTSqol is a psychometrically robust patient-completed questionnaire evaluating quality of life (QoL) in urinary incontinent patients for use in research and clinical practice across the world. The ICIQ-LUTSqol is the King's Health Questionnaire (KHQ) adapted for use within the ICIQ structure and provides a measure to assess the impact of urinary incontinence on quality of life with particular reference to social effects. It is an ideal research tool as it explores in detail the impact on patients' lives of urinary incontinence and can be used as an outcome measure to assess impact of different treatment modalities. [51] The questionnaire is composed of 20 sections with each section asking about the impact of the patient's urinary symptoms on a different aspect of their daily activities and quality of life:
The patient is asked to grade the impact on a scale of 1 to 4 (with an additional 'not applicable' option for some questions), with (4) indicating the greatest impact.
The participant is also asked to grade how much they are bothered by each issue on a scale of 0 – 10, with (0) being 'not at all' and (10) being 'a great deal'.

#### 7.5.5.5. EQ-5D-5L

EQ-5D-5L [52] is a patient completed five item, validated general quality of life measure from which health utility can be calculated. This is a score within the range 0 to 1 for quality of life, where (0) is equivalent to death and (1) represents perfect health.

The EQ-5D-5L consists of two pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS):

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

#### 7.5.5.6. Randomisation treatment choice

As part of the six weeks post-intervention visit participants will be asked whether there were any specific reasons which led them to choose their randomisation treatment options.

#### 7.5.5.7. Healthcare Services

Primary and secondary care resource use will be recorded via a patient completed Healthcare Services questionnaire (either on a paper form or electronically) at screening, baseline (if required), six months, 12 months, two and three years after intervention. Participants will be asked to record each visit and the reason for this.

A micro-costing analysis of each intervention will be conducted to inform the within-trial economic evaluation. The resources used for each surgery will be estimated for each trial participant.

Information on the resources needed for each intervention will be derived from data captured in the eCRF and obtained from the trial team.

#### 7.5.5.8. Time and Travel

Information on patient and carer costs will be collected via a Time and Travel questionnaire administered at 12 months post intervention. The questionnaire includes questions relating to travel time, travel costs and time away from usual activities resulting from attendance to healthcare visits. Within this questionnaire, for each of the main types of contact with NHS services, respondents are asked about their method of transport, travel costs, distance travelled, how long it took to get to the venue, what they would have otherwise been doing at this time, whether they were accompanied (and if so, what that person would have otherwise been doing at the time), and how long they spent in total at their appointment.

All the information gathered via the Time and Travel questionnaire will be summarised and categorised by intervention, type of admission and care received. These costs will then be combined with the information gathered via the Health Care Utilisation questionnaires in order to conduct the economic evaluation from a broader, societal perspective.

#### 7.5.5.9. Acceptability Test

Acceptability of the procedure will be assessed after the procedure at the six months timepoint. Patient acceptability to a surgical procedure has no agreed definition [54] but can be defined as "*appropriateness in addressing the clinical problem, suitability to individual lifestyle, convenience and effectiveness in managing the clinical problem".*[55]

The patient will be asked to answer questions to gauge their feelings of acceptability about their recent surgical procedure using the 'Friends and Family test'; 'Thinking about your procedure overall how was your experience of the procedure?" and 'Please can you tell us why you gave your answer?'

#### 7.5.5.10. Post-Intervention Catheterisation Status

Participants will be asked to answer a question concerning their current catheterisation status at the time of their six months, 12 months, two & three years post-intervention visits. If the participant is currently catheterised when they complete their PROMS at a given post-intervention study visit, then the following questionnaires must not be completed: I-PSS, I-PSS-QOL, ICIQ-MLUTS. The ICIQ-MLUTSsex, ICIQ-LUTSqol, EQ-5D-5L and Healthcare Services questionnaires can still be completed regardless of the participant's catheterisation status.

#### 7.5.5.10. Re-intervention Status (Additional surgical procedures)

Participants will be asked whether they have required any type of surgical re-intervention (and if so details of what intervention has been received) for their urological symptoms since receiving their trial intervention.

#### 7.5.5.11. Hospital Attendance Questionnaire

Information on post-intervention hospital attendance rate will be collected using a hospital attendance questionnaire administered at six months and 12 months post-intervention. Participants will be asked to record the dates of all hospital visits (inpatient and outpatient visits) that they have attended since their intervention for events/conditions possibly associated with BPE, condition progression, intervention (including routine follow-up appointments post-intervention), along with the reason for each visit.

#### 7.5.5.12. Catheterisation Questionnaire

Information on catheterisation use after the 12 months post-intervention visit will be collected using a catheterisation questionnaire administered at the two and three years post-intervention. Participants will be asked to confirm if they have had a catheter at any point since their last trial visit and if so, to provide the insertion and removal dates (if possible), along with the reason for each episode of catheterisation.

### 7.6. Pre-Procedure Checklist

A pre-procedure checklist will be completed by the operating surgeon on the day of intervention to check that the participant remains willing to participate in the trial and that they still meet the eligibility criteria. If the participant no longer meets the eligibility criteria, (e.g. the participant has developed urinary retention and has subsequently been catheterised), then they will be withdrawn from their allocated trial intervention and treated according to the standard of care procedures in place at their local site/UAN. Any concerns about continuing eligibility can be discussed with the CI.

Data will be collected by the operating surgeon via the completion of either a trial specific paper form or via the use of an electronic portal (method of collection determined by the operating site of each UAN).

### 7.7. Operative, Perioperative and Post-operative Parameters

This will encompass the collection of specified operative data by the operating surgeon and perioperative and post-operative data by the participant's research team, from the point of intervention up to 12 months post-intervention.

Operative parameter data collected by the operating surgeon will include: method of anaesthetic, name of operating surgeon, operative time, intraoperative adverse events, location of procedure, (e.g. theatre, urology clinic), where the patient is transferred to after the procedure, (e.g. home, day-case ward, recovery ward), equipment failure, number of intervention items used, change of procedure from original randomisation allocation (if required) and use of any blood products during surgery. As

described in section 7.7., surgeons will have the option of either completing a trial specific paper form or entering the data electronically.

Perioperative and post-operative data will be collected by the designated lead research team within the participant's trial site, up to and including the 12 months post-intervention visit. This will be obtained via discussions between the participant and the research team at the six weeks and six months post-intervention telephone visits and on-site one year post-intervention visit.
Data collected will include:

- Use and duration of catheterisation (if applicable) perioperatively up to six weeks post-intervention and then post-operatively up to and including 12 months post-intervention
- Use of any blood products up to six weeks post-intervention
- Incidents of acute urinary retention post-intervention up to and including 12 months post-intervention
- Details of any surgical re-intervention required (at the six months and 12 months post-intervention visit) as reported in participant questionnaires

If necessary, the participant's medical notes should also be reviewed to aid collection of the required data.

## 7.8. Discharge Summary

Once the patient is discharged from hospital following their surgical intervention, a copy of the discharge summary letter will be sent to the designated lead research team within the participant's trial site. Discharge summary data will be entered into the trial database, this will include length of stay for health economic evaluation, as well as discharge medications.

## 7.9. Adverse Event Review

Participants will receive a telephone call from their designated lead research site at six weeks and six months post-intervention and will be asked to provide details of any adverse events they have experienced since their procedure. This will include details on any hospital attendance (both in-patient or out-patient) associated with BPE, condition progression, intervention or treatment failure, need for further medical input (either in secondary care or via GP), as well as details of any medications taken for adverse events. See section 9.0 for further information on safety reporting including protocol specific reporting exclusions.

## 7.10. Concomitant Medications

The use of prostate specific medications that are used for the treatment of male LUTS due to BPE is permitted although generally these drugs will be stopped after administration of the trial intervention. Certain other medications may need to be stopped as per local site protocol.

Only medications for the control/relief of the following conditions/events will be collected:

- urological symptoms
- pain relief following study intervention

- antibiotics to treat infections post study intervention
- anti-platelet and anti-clotting medication
- all medications associated with adverse events as defined in section 9.2.

Drug names, indications and start & end dates of concomitant medications for each participant will be collected during the trial by the research site staff at all visits between the on-site screening visit, and the on-site 12 months post-intervention visit.

## 7.11. Gift Vouchers

On return of the completed patient questionnaires at two and three years post-intervention, patients will be sent a gift voucher as a thank you for their participation.

## 7.12. Schedule of Events

| | **Screening** | **Baseline** (within 3 months prior to procedure) | **Procedure** | **6 weeks post-procedure** (+/-1 week) | **6 months post-procedure** (+/- 1 month) | **12 months post-procedure** (+/- 1 month) | **2 years post-procedure** (+/- 1 month) | **3 years post-procedure** (+/- 1 month) |
|---|---|---|---|---|---|---|---|---|
| **Type** | **On-site** | **Remote** | **On-site** | **Remote + phone** | **Remote + phone** | **Remote + On-site** | **Remote** | **Remote** |
| **Consent** (must be done prior to any assessments) | **X** | | | | | | | |
| **Demographics and Medical History** | **X** | | | | | | | |
| **Prostate Volume** | **X**[a] | | | | | | | |
| **Digital Rectal Exam** | **X**[b] | | | | | | | |
| **Eligibility** | **X** | | | | | | | |
| **Randomisation** | **X** | | | | | | | |
| **Give out Post-Intervention Participant Diary** | **X** | | | | | | | |
| **Flow Test and Post Void Residual** | **X**[c] | | | | | **X** | | |
| **Pre-Procedure Checklist** | | | **X** | | | | | |
| **Operative Parameters** | | | **X**[d] | | | | | |
| **Perioperative Parameters** | | | | **X** | | | | |
| **Post-Operative Parameters** | | | | | **X** | **X** | | |
| **Discharge Summary** | | | **X** | | | | | |
| **Adverse Events** | | | **X** | **X** | **X** | | | |
| **Concomitant Medication** | **X** | | **X** | **X** | **X** | **X** | | |

| | **Screening** | **Baseline** (within 3 months prior to procedure) | **Procedure** | **6 weeks post-procedure** (+/-1 week) | **6 months post-procedure** (+/- 1 month) | **12 months post-procedure** (+/- 1 month) | **2 years post-procedure** (+/- 1 month) | **3 years post-procedure** (+/- 1 month) |
|---|---|---|---|---|---|---|---|---|
| **Type** | **On-site** | **Remote** | **On-site** | **Remote + phone** | **Remote + phone** | **Remote + On-site** | **Remote** | **Remote** |
| **Patient Reported Outcomes** (electronic or paper) | | | | | | | | |
| **Post-intervention catheterisation status** | | | | | **X**[e] | **X**[e] | **X**[e] | **X**[e] |
| **Re-intervention status** | | | | | **X** | **X** | **X** | **X** |
| **Hospitalisation Attendance Questionnaire** | | | | | **X** | **X** | | |
| **Catheterisation Questionnaire** | | | | | | | **X** | **X** |
| **I-PSS inc Qol** | **X**[f] | **X**[f] | | | **X** | **X** | **X** | **X** |
| **EQ-5D-5L** | **X**[f] | **X**[f] | | **X** | **X** | **X** | **X** | **X** |
| **Randomisation treatment choice** | | | | X | | | | |
| **ICIQ-MLUTS** | **X**[f] | **X**[f] | | | **X** | **X** | **X** | **X** |
| **ICIQ-MLUTSsex** | **X**[f] | **X**[f] | | | **X** | **X** | **X** | **X** |
| **ICIQ-LUTSqol** | **X**[f] | **X**[f] | | | **X** | **X** | **X** | **X** |
| **Healthcare Services** | **X**[f] | **X**[f] | | | **X** | **X** | **X** | **X** |
| **Time and Travel** | | | | | | **X** | | |
| **Acceptability Test** | | | | | **X** | | | |

[a]Where not available from standard of care within 12 months prior to consent

[b]Where cancer has not previously been excluded by either DRE, or MRI, or a negative biopsy within 12 months prior to consent.

[c]To be done at screening if not measured in the previous six months prior to consent. Flow test and post void residual can **either** be completed at the end of the screening visit once eligibility has been confirmed (if this is convenient for both the patient and research team), or at a separate visit before the procedure within six weeks of screening, if more convenient.

[d]For completion both pre- and post-surgery.

[e]If patient is catheterised at this timepoint then the following PROMS should not be completed; I-PSS, I-PSS-QOL and ICIQ-MLUTS

[f]Screening PROMS must be completed prior to randomisation. In the event that the time between completing the questionnaires and receiving the intervention is greater than six months, the questionnaires will need to be repeated within three months prior to the procedure.

## 7.13. Withdrawal and Discontinuation

The investigator may discontinue a participant from their allocated trial intervention or withdraw them from the trial at any time if the investigator considers it necessary. Advice from the Chief Investigator should be sought where needed. The participant may also discontinue from aspects of the study or withdraw consent to continue in the study at any time. See the relevant criteria below. The reason for discontinuation or withdrawal should be documented in the trial database eCRF and the participant's medical notes.

### 7.13.1. Withdrawal Criteria

Participants have the right to withdraw from the trial at any time without having to give a reason. The investigator should complete an investigator led withdrawal form on behalf of the participant. If available, the reason for withdrawal should be documented on the paper withdrawal form, the trial database eCRF and the participant's medical notes. Participants who withdraw from the trial will not be replaced.

If a trial participant withdraws from the trial, all data collected up to the point of withdrawal will be retained and included in the analysis. Routine NHS data will also be collected for the trial up to the three year visit timepoint, unless a participant asks for this to stop. Consent for this will be sought on the withdrawal form. A list of possible routine data to be collected is described in the Operative, Perioperative and Post-Operative Parameters section 7.8

Discontinuation from an aspect(s) of the study (as per section 7.14.2.) is preferable to a withdrawal however, in situations where this is not appropriate or feasible, the Investigator can decide to withdraw the participant entirely. Reasons for an Investigator led withdrawal can include an adverse event that renders the participant unable to continue in any aspect of the trial, or where the participant is unable to comply significantly with trial requirements. Advice from the Chief Investigator should be sought where needed.

When an investigator withdraws a participant from the trial they should also complete an investigator led withdrawal form. The participant must be informed of the investigator decision and their return to their routine care pathway in the NHS.

### 7.13.2. Discontinuation criteria

If a randomised participant declines their allocated intervention, they can remain in the trial and complete all follow-up visits as part of the intention to treat analysis, as long as the patient is willing to be followed up as per the study requirements. If an intervention date had not been scheduled (and no alternative trial intervention is performed) then follow-up timepoints should be measured from the date of randomisation. In all cases, it should be documented in the trial database eCRF and the participant's medical notes that they have declined their randomised intervention. This would not be considered a withdrawal of consent but would be regarded as a discontinuation of their allocated intervention.

If a randomised participant does not want to attend any follow-up visits but is willing to continue to complete the trial questionnaires (or vice versa), they may continue in the study. This would not be

considered a withdrawal of consent but would be regarded as a discontinuation of an aspect of the trial follow-up.

All participant discussions regarding any aspect of discontinuation should be clearly documented in the patient notes, with ongoing consent for the study documented when necessary. It is possible, due to the period of time between consent and surgery, some participants may no longer meet the eligibility criteria at the time of the intervention. As stated in section 7.7., a pre-procedure checklist will be completed by the operating surgeon on the day of intervention to check that the participant remains willing to participate in the trial and still meets the eligibility criteria. If the participant no longer meets the eligibility criteria, then they will be discontinued from their allocated trial intervention and treated according to the standard of care procedures in place at their site. They may still continue with the trial follow-up if they are willing. Follow-up timepoints should be measured from the planned date of intervention.

### 7.14. End of Trial

The trial will end after the last patient's last visit (data collection timepoint).

### 7.15. Post Trial Care

At the end of their participation in the study participants will continue to receive standard NHS care. Where a participant has been referred from a PIC site, they may remain under the care of the team at the research site hospital trust for standard care follow up post intervention.

# 8. TRIAL INTERVENTION

Participants will receive one of the following interventions:

I. Prostatic urethral lift (PUL)

II. Rezum

III. Temporary Implantable Nitinol Device (iTIND)

IV. TURP

Please see section 2. Rationale.

### 8.1. Training and Competence

All participating surgeons will have completed a mandated training pathway, including at least 10 cases for PUL and Rezum, and five cases for iTIND since completing training. Confirmation of completion of these minimum case numbers should be recorded on the trial surgical training log prior to the surgeon performing any MIT as part of the PREMISE trial. Additionally, we will record the number of cases performed by each surgeon for each MITS in their career prior to their participation in the PREMISE trial, allowing for further analysis of surgeon experience. During the trial we will record details of which surgeon performs each procedure, and the total, by surgeon, for each.

A surgeon in training may perform the procedure or part of it, provided that they are under the direct supervision of a surgeon who has completed the above mandated training pathways and who has been appropriately delegated the task of performing the procedure by the PI (as documented via the delegation log).

### 8.2. Known Risks

Please see Assessment of Expectedness in section 9.3.3 for list of potential side effects for each intervention.

# 9. SAFETY REPORTING

## 9.1. Definitions

| Term | Definition |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a participant, including occurrences which do not necessarily have a causal relationship with the study procedures/intervention |
| Adverse Reaction (AR) | An AE where there is evidence to suggest there is a causal relationship between the event and the study procedures/ intervention. |
| Serious Adverse Event (SAE) | Any untoward medical occurrence that:<br>• Results in death<br>• Is life-threatening*<br>• Requires inpatient hospitalisation or prolongation of existing hospitalisation<br>• Results in persistent or significant disability/incapacity<br>• Consists of a congenital anomaly or birth defect<br>• is otherwise considered medically significant by the investigator<br>* - life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. |
| Related Serious Event | An SAE where there is evidence to suggest there is a causal relationship between the event and the study procedures/intervention. |
| Unexpected Related Serious Event (URSE) | An SAE where there is evidence to suggest there is a causal relationship between the event and the study procedures/intervention, where the event is unexpected |

## 9.2. Adverse Events

### 9.2.1. Recording Adverse Events

It is intended that all AEs occurring from the point of surgical intervention until six months post-surgery possibly associated with BPE, condition progression, intervention or treatment failure are collected as adverse events. These events must be recorded in the trial database eCRF and recorded in the participant's medical notes as part of their ongoing care. The Clavien Dindo criteria in section 9.2.3. should be used for Assessment of Severity.

All intraoperative AEs will be recorded and identified via a question in the Operative Parameters form and post-operative AEs will be patient reported by an adverse events questionnaire administered at the telephone call at six weeks and six months post-surgery or identified through medical records.

The documentation of each AE should include an event term, event duration (start and stop dates) and details of any action taken or treatment in response to the event. Each AE must be assessed by the site PI or delegated investigator for severity (section 9.2.3.), seriousness (section 9.2.4.) and causality (section 9.2.5.).

### 9.2.2. Exclusions to Adverse Events reporting

For the purposes of this trial, AEs not related to the condition or the intervention will not be collected, including but not limited to hospitalization for the non-related conditions.

### 9.2.3. Assessment of Severity

The PI, or delegated clinician, should make an assessment of severity for each AE according to the following Clavien Dindo [56] criteria as shown in the table below:

| Grade | Definition |
|---|---|
| I | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions<br>Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at bedside. |
| II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications<br>Blood transfusions and total parenteral nutrition are also included |
| III Requiring surgical, endoscopic or radiological intervention: | |
| IIIa | Intervention not under general anaesthesia |
| IIIb | Intervention under general anaesthesia |
| IV Life threatening complication (including CNS complications)* requiring IC/ICU management: | |

| Grade | Definition |
|---|---|
| IVa | Single organ dysfunction (including dialysis) |
| IVb | Multiorgan dysfunction |
| V | Death of a patient |

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.

#### 9.2.4. Assessment of Seriousness

The PI, or delegated clinician, should make an assessment of seriousness against the standard definition in the Safety Reporting Definitions section 9.1.

#### 9.2.5. Assessment of Causality

The relationship between the intervention and the occurrence of each AE must be assessed and categorised by the PI or delegated clinician using clinical judgement to determine the causal relationship. Other factors such as medical history of underlying diseases, concomitant therapy and any other relevant risk factors should be considered. The assessor should also consult the expected events in section 9.3.1. If there is any doubt, the CI may be consulted. The following definitions should be used:

| | |
|---|---|
| Yes (related) | The event is considered related or possibly related to the intervention |
| No | The event is not considered related to the intervention |

### 9.3. Expedited Safety Reporting

The safety profile of the four interventions is well-established within this patient population and a list of expected events can be found in section 9.3.3. Immediate reporting of expected SAEs to the Sponsor is not required, only unexpected SAEs related to the intervention require expedited safety reporting. All adverse events (including expected and unexpected SAEs) should be recorded in the eCRF (Sealed Envelope) and will be reviewed by the Data Monitoring Committee on a regular basis (see section 13.1).

#### 9.3.1. Reporting SAEs

Where an AE is assessed as serious, related to the intervention and uunexpected according to the protocol section 9.3.3, it must be reported immediately. Unexpected, related serious adverse

events, URSEs should be reported from the point of surgical intervention until six months post-surgery.

**Please send completed SAE report forms via secure email to:**
**nctu.premise.sae1@nhs.net**

This is a distribution list to ensure that all relevant individuals (CI, NCTU trial management and QA management personnel and Sponsor) are informed of the event in a timely manner. All confirmed URSEs will be allocated a unique code number and a confirmation of receipt returned to the sender. URSEs will be recorded by trial management personnel on the trial's safety database.

To ensure adherence with the required reporting timeframes, sites must notify NCTU of URSEs immediately but no later than 24 hours after becoming aware. Information should be submitted on an SAE report form via secure e-mail. Examples of secure email include nhs.net and nhs.uk where listed as accredited to the DCB1596 secure email standard, (https://digital.nhs.uk/services/nhsmail/the-secure-email-standard). Where it is not possible to send a report via a secure e-mail, the report should be sent encrypted.

Preliminary reporting to NCTU via email or telephone is acceptable in order to meet the 24 hour reporting timeline, where circumstances do not allow for immediate completion of the SAE form. However the SAE form should be completed and submitted as soon as possible after the initial notification in order to comply with reporting timelines.

For each URSE the following information will be collected:

- Event term
- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Severity
- Action taken
- Outcome
- Seriousness criteria
- Causality & Expectedness in the opinion of the investigator

In the case of incomplete information at the time of initial reporting, or change of condition or follow up information, a follow up report form must be completed and sent via secure email as soon as possible. All URSEs will be followed up until resolution, or until the participant reaches the end of the study. An URSE is considered to have resolved if the outcome has been classed as:

- Completely Recovered
- Recovered with Sequelae
- Condition stable and no change anticipated
- Participant Died

The assessment of causality and expectedness will undergo documented review by the PI and CI for each URSE.

If a participant withdraws from the study due to an URSE, the trial team should continue to follow up the event until the URSE has resolved or stabilised.

### 9.3.2. Exclusions to SAE reporting

Any AEs that are serious and not-related to the intervention, or that are serious, related to the intervention and expected (as per protocol section 9.3.3.) do not require immediate (24-hour) reporting. Events that are excluded from recording as an AE for the study should not be reported as SAEs i.e. SAEs not related to the condition or the intervention, including death (see section 9.5)**.** Planned hospital admissions for the study intervention are also excluded from safety reporting.

### 9.3.3. Assessment of Expectedness

All related serious events (SAEs determined as having reasonable suspected causal relationship between the event and the study intervention) will be assessed for expectedness by both the PI and the CI using the list of expected events below:

| **TURP** | |
|---|---|
| Bladder/ abdominal pain | Retained fragments |
| Bladder neck stenosis | Retrograde ejaculation |
| Bladder perforation | Return to theatre for bladder wash out for bleeding |
| Capsular perforation | |
| Clot retention | Stress incontinence |
| Dysuria | TUR-syndrome |
| Erectile dysfunction | Urethral stricture |
| Haematuria | Urinary frequency |
| Hemorrhage | Urinary incontinence |
| Injury to the urethra | Urinary retention |
| Passage of debris in urine | Urinary tract infection |
| Passing of clots in urine | Urosepsis |
| Penile pain | |

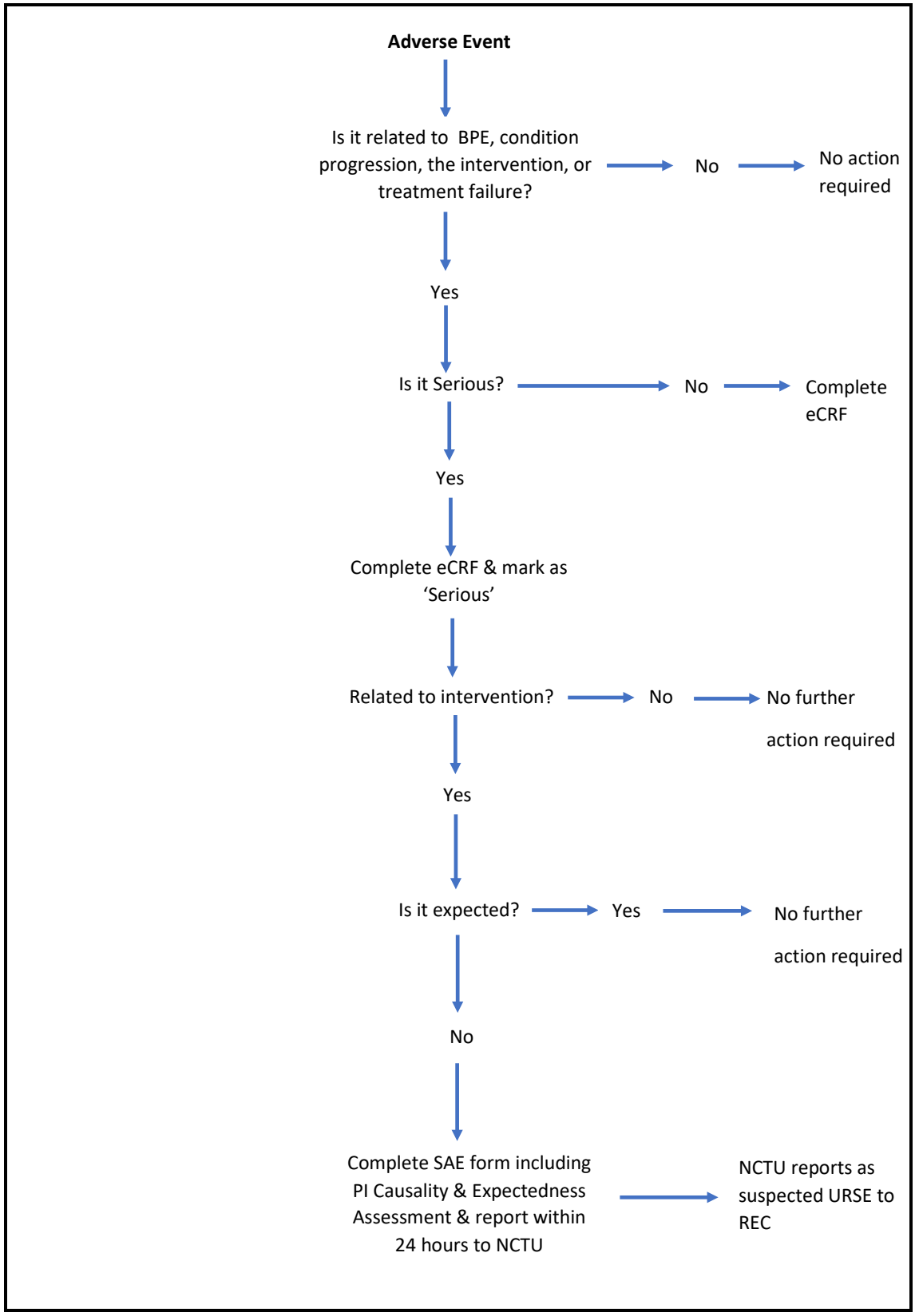
| **Rezum** | |
|---|---|
| Dysuria | Return to theatre for resection of prostate |
| Erectile dysfunction | Sediment / debris in urine |
| Haematuria | Urethral stricture |
| Hematospermia | Urinary frequency |
| Pain or discomfort in the pelvic area | Urinary incontinence |
| Passing of clots | Urinary leakage |
| Penile pain | Urinary retention |
| Prostate abscess | Urinary tract infection |
| Retrograde ejaculation | Urinary urgency |
| **iTIND** | |
| Bladder neck stricture | Penile pain |
| Bladder perforation | Pyrexia |
| Changes to erectile function | Retrograde ejaculation |
| Dysuria | Return to theatre for wash out / bleeding |
| Haematuria | Removal required under general anesthetic |
| Hematospermia | Urethral stricture |
| Hemorrhage | Urinary frequency |
| Inflammation to the bladder neck | Urinary hesitancy |
| Inflammation to the prostatic urethra | Urinary incontinence |
| Irritation to the meatus | Urinary leakage / incontinence |
| Local irritation | Urinary retention |
| Pain or pressure in the perineal area | Urinary tract infection |
| Pelvic discomfort | Urinary urgency |
| **PUL** | |
| Dysuria | Return to theatre for wash out / bleeding |
| Erectile dysfunction | Temporary urinary urge incontinence |
| Haematuria | Urethral stricture |
| Implant encrustation | Urinary incontinence |
| Misfire of implant / Bone strike | Urinary leakage |
| Pain or discomfort in the pelvic area | Urinary retention |
| Passage of clots/ debris | Urinary tract infection |
| Pelvic haematoma | Urinary urgency |
| Penile pain | |
| Retrograde ejaculation | |

| **Anesthesia associated events** | |
|---|---|
| Allergic reaction<br>Aspiration<br>Chest infection<br>Death<br>Deep Vein Thrombosis<br>Drug reaction<br>Heart Attack<br>Local inflammation / skin reactions / cellulitis | Nausea & Vomiting<br>Nerve injury<br>Pain and conscious awareness<br>Paralysis<br>Pulmonary embolus<br>Sore throat and hoarse voice<br>Spinal haematoma<br>Stroke |

### 9.3.4. Safety Reporting Summary Table

| **Event** | **Required actions** |
|---|---|
| Adverse Event | Record in eCRF |
| SAE that is related to BPE, condition progression or treatment failure | Record in eCRF and mark as serious |
| SAE that is related to the intervention and is expected (as per protocol section 9.3.1) | Record in eCRF and mark as serious |
| SAE that is related to the intervention and is **unexpected** (as per protocol section 9.3.1) | Record in eCRF and mark as serious<br><br>Report immediately to NCTU as a suspected URSE on an SAE Report Form via secure email |
| (Serious) Adverse Event **not** related to intervention, BPE, condition progression or treatment failure | None (will not be collected for this study) |

### 9.3.1. Safety Reporting Diagram




Contact details for reporting SAEs

Please send SAE form(s) via secure email to **nctu.premise.sae1@nhs.net**

## 9.4. Reporting URSEs to the REC

All URSEs occurring from the intervention until six months post-trial intervention must be reported to the NHS Research Ethics Committee (REC). The NCTU will perform this reporting and notify the Sponsor.

URSEs must be reported no later than 15 calendar days after the NCTU has first knowledge of the event. Any relevant follow-up information should be sought and reported as soon as possible after the initial report.

The reporting timeframe starts at day 0 when the NCTU is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- Patient trial number
- Name of intervention
- Date of notification of the event
- Medical description of the event
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

The site is expected to co-operate fully with NCTU and Sponsor staff, to ensure that a full and detailed report is submitted to the REC within the required timelines. PIs will be informed of all URSEs by NCTU.

## 9.5. Notification of Deaths

AEs with an outcome of death, that are related to the study intervention and unexpected will be reported as an URSE to NCTU on an SAE form. Other deaths resulting from AEs that are either related to the intervention and expected, or are related to BPE, condition progression, or treatment failure will be recorded in the eCRF and marked as 'serious'. Deaths for reasons that do not meet the criteria to be recorded as an AE (as described in 9.2.2.) will not be recorded in the eCRF

## 9.6. Pregnancy Reporting

Reporting of pregnancy of partners of participants is not required for this trial.

## 9.7. Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, NCTU must be notified immediately and details of the USM given. The NCTU must inform the NHS REC within three days of the USM taking place in accordance with the Sponsor's standard operating procedures.

### 9.8. Responsibilities

***Principal Investigator***

- Ensuring that AEs are recorded in line with the requirements of the protocol.
- Using medical judgement in assessment of severity, seriousness and causality of AEs.
- Perform assessment of expectedness of all intervention-related SAEs
- Ensuring that all URSEs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- These tasks may be delegated to a member of the research team, but the PI retains overall responsibility.

***Chief Investigator***

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit
- Using medical judgement in assessment of severity, seriousness and causality of SAEs where it has not been possible to obtain local medical assessment.
- Perform assessment of causality and expectedness of all related SAEs on behalf of Sponsor.
- Immediate review of all URSEs.
- Review of specific SAEs and URSEs in accordance with the trial risk assessment and protocol.
- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all AEs and SAEs.
- Reviewing expected events at least annually

***Sponsor***

- Data collection and verification of all AEs onto a database (may be delegated to NCTU).
- Assessment of expectedness of any related serious events (may be delegated to CI).
- Expedited reporting of URSEs to the REC within required timelines (may be delegated to NCTU).
- Reporting of USMs to REC within required timeline (may be delegated to NCTU).
- Notification of all investigator sites of any URSE that occurs (may be delegated to NCTU).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ration throughout the life of the trial (may be delegated to NCTU).

***TSC/DMC***

- Review of safety data collected to date to identify any trends

# 10. STATISTICAL CONSIDERATIONS

Full details of all statistical analyses will be pre-specified in a statistical analysis plan which will be written and approved prior to release of any unblinded data to the senior and trial statisticians.

The trial statistician and senior trial statistician will be unblinded for the purposes of producing and reviewing reports to the Data Monitoring Committee (DMC). Unblinded reports will be kept confidential and will only be viewed by the DMC members and the senior and trial statistician. The statistical analysis plan will be written and approved by the senior and trial statistician prior to any access to unblinded outcome data. A statistical methodology advisor will also be involved in the trial

and will remain blinded to outcome data until data lock for the primary analysis. Should any amendments to the statistical analysis plan be required after the senior and trial statisticians have accessed unblinded outcome data these can be reviewed and approved by the blinded statistical methodology advisor.

## 10.1. Analysis Populations

The following analysis populations are defined for the purpose of analysis:

| Analysis Population | Description |
|---|---|
| Intention-to-treat (ITT) | Includes all randomised participants, analysed according to randomised treatment allocation. |
| Modified intention-to-treat | Includes all randomised participants, continuing to meet the eligibility criteria at the time of intervention, analysed according to randomised treatment allocation. |
| Per-protocol | Includes all randomised participants receiving their allocated intervention and continuing to meet the eligibility criteria at the time of intervention, analysed according to randomised treatment allocation. |
| As-treated | Includes all randomised participants receiving one of the trial interventions and continuing to meet the eligibility criteria at the time of intervention, analysed according to treatment received. |
| Safety | Includes all randomised participants receiving a trial intervention, analysed according to the intervention received. |

For the main analysis of efficacy outcomes, participants will be analysed according to their randomised treatment allocation; whereas safety data and post-operative complications will be reported and analysed according to the intervention they actually received.

## 10.2. Sample Size Calculations

The primary outcome is the change in I-PSS total score between baseline and 12 months. The trial is powered to test the non-inferiority (NI) of each experimental arm to the TURP arm in terms of I-PSS. The three null hypotheses to be tested are:

i. The mean difference in 12-month I-PSS total score (adjusted for baseline) between PUL and TURP is > 3

ii. The mean difference in 12-month I-PSS total score (adjusted for baseline) between Rezum and TURP is > 3

iii. The mean difference in 12-month I-PSS total score (adjusted for baseline) between iTIND and TURP is > 3

To test each hypothesis, participants will be pooled across the following randomisation schemes:

| i. TURP vs PUL | ii. TURP vs Rezum | iii. TURP vs iTIND |
|---|---|---|
| TURP: PUL: Rezum: iTIND | TURP: PUL: Rezum: iTIND | TURP: PUL: Rezum: iTIND |
| TURP: PUL: Rezum | TURP: PUL: Rezum | TURP: PUL: iTIND |
| TURP: PUL: iTIND | TURP: Rezum: iTIND | TURP: Rezum: iTIND |
| TURP: PUL | TURP: Rezum | TURP: iTIND |

In data from the UNBLOCS trial (NIHR HTA 12-35-15) [33] the standard deviation (SD) of the I-PSS score at 12-months follow-up was 6.3 (based on the non-catheterised participants with complete data).

A non-inferiority margin of three points is used. This represents the minimally clinically important difference (MCID) for the outcome.[4,46,47] The non-inferiority hypothesis is equivalent to ruling out TURP providing an improvement of the MCID or greater against a minimally invasive treatment.

Assuming a minimally invasive arm has the same mean I-PSS as TURP, standard non-inferiority sample size formula suggests we would require 12-month information on 100 participants per intervention for each comparison for 90% power to conclude non-inferiority at a one-sided type I error rate of 0.0195 (nQuery). This p-value threshold yields a maximum chance of falsely concluding non-inferiority of 5% assuming a Dunnett correction.

We have inflated this sample size to account for a 25% attrition rate, which was seen in UNBLOCS for patient-reported outcomes. This gives a sample size of 134 participants per intervention for each comparison. Since we are adjusting for baseline I-PSS, we would expect power to be higher than 90%.

The minimum required sample size will therefore be 536 participants, however due to the nature of the personalised randomised design, not all participants will contribute to each analysis, and it is likely that over-recruitment will be required to obtain a sufficient number of participants receiving each intervention for each comparison. The number of participants recruited into each randomisation scheme and the number of participants available for each analysis will be closely monitored by the Trial Management Group. If it becomes apparent that low numbers of participants are being recruited to one intervention, such that the power likely to be achieved for comparisons involving that arm are substantially reduced, the utility of continuing to recruit to randomisation schemes containing that intervention will be evaluated and discussed with the DMC, TSC and Funder. In the event it is not feasible to recruit a sufficient number of participants to TURP we will consider utilising historical control data from previously conducted randomised controlled trials.

## 10.3. Statistical Analyses

### 10.3.1. Analysis of the Primary Outcome Measure

**Main analysis methods**

The main primary objective is to estimate the mean difference in the change in the I-PSS symptom score from baseline to 12 months in men requiring surgery for BOO treated with each MIT compared to TURP assuming all eligible patients would adhere to their randomised treatment allocation.

The main primary estimand is described by the following attributes:

| Estimand attribute | Description |
|---|---|
| Population | Patients offered surgery for BOO and meeting the PREMISE eligibility criteria |
| Treatment conditions | Intervention via PUL, iTIND, Rezum (MITS) vs TURP (Control) |
| Outcome measure | Change in I-PSS score from baseline to 12-month follow-up |
| Strategies used to handle intercurrent events | • Becoming ineligible between randomisation and intervention - principal strata[1]<br>• Not undergoing randomised treatment – hypothetical[2] |
| Population-level summary measure | Mean difference in I-PSS score at 12 months (adjusted for baseline) between each MITS and TURP |

*[1]The principal strata strategy targets the treatment effect within the subgroup of patients who would not have the intercurrent event, regardless of allocated treatment group*

*[2]The hypothetical strategy targets the treatment effect in the hypothetical setting where the intercurrent event did not occur*

For the pairwise comparison of each MIT to TURP data will be pooled across randomisation schemes as shown in Section 10.2.

If, within each comparison, the proportion of eligible participants not undergoing their allocated treatment is >5% in either randomised treatment group inverse probability weighting (IPW) will be used to estimate the average causal effect of each MIT compared to TURP in the hypothetical setting where all eligible participants adhere to their allocated treatment. This will be implemented in two stages. In the first stage, a logistic regression model will be fitted separately to each randomised treatment group with adherence to assigned treatment as the outcome (dependent variable) and pre-specified baseline measures as covariates (to be identified following a review of literature and expert opinion and agreed prior to data lock for the main analysis). The modified ITT population will be used, with all participants continuing to meet the eligibility criteria included. These models will be used to calculate weights (the inverse of participant specific predicted probabilities of adhering to allocated treatment) to be used in the main analysis model (second stage).

The main analysis will be carried out in the per-protocol population. A linear mixed-effects model (mixed model for repeated measures) will be fitted to the six- and twelve-month I-PSS total score data, with fixed effects for baseline I-PSS, randomisation scheme, and a treatment-by-time interaction term. Random effects for site (this will be the Hub where a Hub and Spoke model is used) and individual (nested within site) will be used. Where required, the model will be weighted using the weights calculated as described above.

The estimated difference between control and each experimental treatment at 12 months will be extracted from the model and reported with 95% confidence intervals. Adjusted 95% CI will also be provided as supplementary information. The one-sided p-value for non-inferiority (with margin three) will be calculated. The critical p-value threshold will be set as 0.0195 so that the maximum chance of incorrectly concluding an arm is non-inferior when they all are inferior is 5% (following the Dunnett procedure).

The experimental arms will be compared to one another for the primary outcome, although the trial is not powered for this comparison.

**Sensitivity analyses**
Where IPW methods are used for the main analysis the analysis will be repeated without the use of IPW methods.

**Supplementary analyses**
Analyses will be repeated in the as-treated, modified ITT and ITT populations. We will also estimate the Complier Average Causal Effect (CACE) using Instrumental Variable (IV) methods.

We will also repeat the main analysis but with participants pooled across all 11 randomisation schemes. Appropriate methods, e.g. weighting procedures, will be used to account for any differences in patient-level variables between arms.

### 10.3.2. Analysis of the Secondary Outcome Measures

Secondary efficacy outcomes will be analysed for superiority of each experimental treatment against control. For each pairwise comparison data will be pooled across randomisation schemes as shown in Section 10.2. Estimated differences between treatment groups will be reported with 95% confidence intervals and two-sided p-values. Analyses will primarily be performed in the per-protocol population (with IPW used where required). Analyses may also be repeated using alternative analysis populations.

Secondary patient-reported outcome measures (including ICIQ-MLUTS – voiding score and incontinence score, ICIQ-MLUTSsex total score, ICIQ-LUTSqol total score, I-PSS-QOL score) up to three years will be analysed using similar linear mixed-effects regression models as described above for the primary outcome measure, but with the baseline value corresponding to the relevant questionnaire included as a fixed effect rather than the baseline I-PSS. Additional scores or items from patient-reported outcome measures may also be reported and analysed using suitable mixed-effects regression models.

Bladder voiding efficiency (BVE) and maximum flow rate (Qmax) at 12 months will be analysed using a linear mixed-effects models, including site as a random effect (this will be the Hub where a Hub and Spoke model is used) and treatment group, randomisation scheme, and baseline measures of the outcome variable of interest as fixed effects.

Length of hospital stay will also be analysed using a linear mixed-effects models, including site as a random effect and treatment group and other stratification factors as fixed effects.

Duration of perioperative catheterisation will be measured as the time from intervention to stopping catheter use. Where a catheter is not required this will be set to zero. Data will be analysed using either a Cox proportional hazards or linear regression model with mixed-effects (including site as a random effect and treatment group and randomisation scheme as fixed effects), depending on whether any censoring is present.

The proportion of participants requiring a blood transfusion will be analysed using a mixed-effects logistic regression model, including site as a random effect and treatment group and randomisation scheme as fixed effects.

The proportion of participants requiring a readmission, experiencing acute urinary retention, requiring a catheter, or re-intervention during follow-up will be analysed using mixed-effects logistic regression models, including site as a random effect and treatment group and randomisation scheme as fixed effects. Time to readmission, catheterisation, acute urinary retention or re-intervention may also be analysed using a Cox proportional hazards model, depending on the number of events observed. Where there are multiple incidences of these outcomes per participant, the data may also be analysed using suitable models for count data, as appropriate for the distribution of the data. Further details will be provided in the statistical analysis plan.

Safety outcomes, including early post-operative symptoms and post-surgical complications will be analysed in the safety population according to the intervention received. Complications will be tabulated by type and severity, with the number and proportion of participants affected and the total number of occurrences reported.

### 10.3.3. Missing data

Analyses using mixed-effects models will give inference that is valid under a missing at random (MAR) assumption. If there is substantial differential dropout between arms then we will apply sensitivity analyses to explore robustness of results to missing not at random (MNAR) mechanisms.

### 10.3.4. Subgroup Analyses

For the primary outcome we will explore subgroup effects through inclusion of an interaction parameter in the primary analysis model. Variables we will consider are:

- Age
- Prostate size
- Symptoms based on I-PSS
- Flow rate
- Voiding efficiency

Full details of all analyses will be pre-specified in the statistical analysis plan.

### 10.3.5. Health Economics Analysis

An important part of this study is how these new MITS perform against existing technologies within the NHS, both in clinical efficacy and with regards to their cost and cost-effectiveness to the NHS. The economic evaluation will comprise (1) a within trial analysis (WTA) in the form of a cost utility analysis based on incremental cost per QALY gained at 12 months, using responses to the EQ-5D 5L questionnaire (2) a longer term model extrapolating costs and outcomes over a lifetime time horizon and (3) the assessment of patient preferences in the form of a contingent valuation survey or discrete choice experiment to enable a cost-benefit analysis (CBA) where costs and outcomes are valued in commensurate units. Additional secondary analysis will be conducted to generate cost-effectiveness estimates at two years and three years post-intervention.

Data collection from the trial will estimate the cost of the interventions (micro costed) and subsequent use of health services captured over the duration of the trial using assessment of health utilisation, at baseline, six months-, 12 months-, two- and three-years post-intervention. The perspective taken in

our base-case analysis will be that of the NHS and PSS. However, a broader perspective will also be explored which will include costs borne by participants/families captured via a time and travel questionnaire. The timing of this questionnaire will be set at 12 months only to minimise respondent burden. All relevant costs associated with providing treatment and subsequent management will be measured. Unit costs will be derived using routine data sources [57 - 59] and study specific estimates. Discounting of both costs and outcomes will be applied [35] where appropriate. Data on the cost of the intervention and subsequent use of services will be combined with unit costs to produce a cost for each trial participant. From these a mean cost per patient per intervention will be calculated from an NHS perspective. A mean cost taking into account patient incurred costs will likewise be estimated. This information will then be used to subsequently derive QALYs and ICERs. As per the statistical analysis (Section 10.2.), should recruitment to TURP be considered insufficient, we will consider utilising historical control data from previously conducted randomised controlled trials

### 10.3.6. The Within Trial Analysis (WTA)

The base case within trial analysis will compare changes in health-related QoL, based on responses to the EQ-5D-5L at baseline, six weeks, six and 12 months. Responses to the EQ-5D-5L will be combined with a UK tariff that is relevant at the time the study reports and used to estimate QALYs. The results of the analyses will be presented as point estimates of mean incremental costs and QALYs. An adjusted analysis will be used to estimate the point estimates of the mean incremental costs, effects and cost-effectiveness using seemingly unrelated regression (SUR). We will explore the uncertainty in estimates of cost-effectiveness through a stochastic sensitivity analysis drawing bootstrapped samples of mean costs and mean QALYs. Results from this analysis will be combined willingness-to-pay (WTP) threshold values generating cost effectiveness acceptability curves (CEACs) that represent the probability of the interventions being cost-effective at each WTP value. As part of the CEA we will also estimate the distribution of costs and health benefits (QALY gains) by socio-economic status using IMD data.

Secondary analysis will be conducted and the cost-effectiveness analysis will be replicated at two and three years post-intervention.

### 10.3.7. Longer-Term Economic Model

Longer term model: The timeline of the trial may not capture all of the costs and health outcomes associated with the interventions. Hence, a decision model will also be developed to estimate costs and outcomes over the lifetime of the patient. The model will be developed in accordance with the NICE reference case (Methods for NICE technology appraisals). [35] Data from the trial will be the main source of data for this, but further data will be derived from the literature and clinical input. The economic model will be used to quantify the uncertainties facing decision-makers and to help inform decisions about the direction of future research. This will be explored using variants of value of information analysis. The results of these analyses will be presented as point estimates of mean incremental costs, and QALYs and incremental cost effectiveness ratios. The model will be consistent with good practice guidelines. [36] The data from the trial will be the main source of data for the model, but further data will be systematically derived from the literature and from expert clinical input. The model will be developed in accordance with the NICE reference case. We anticipate that the model will take the form of a Markov-type, state transition model although the

precise structure of the model will be developed during the project and will reflect the clinical decision question and the course of the condition.

### 10.3.8. Cost Benefit Analysis (CBA)

QALYs may not fully represent patients' preference for treatments and their associated outcomes. We will conduct a preference study in the form of either a contingent valuation (CV) survey or discrete choice experiment (DCE) (the method used will be determined as part of the study) to elicit patient preferences. Both designs will enable the estimation of respondents' willingness to pay for different treatment options and their associated outcomes. Results will enable a cost-benefit analysis to be conducted and will be presented as incremental net benefits. Both stochastic and deterministic sensitivity analyses will be conducted, with the results presented as incremental net benefit curves, alongside the probability that each treatment would be considered cost effective.

Missing data is expected and the methods of imputation used to deal with missing data will be determined once the full trial dataset is available. For all economic analyses, deterministic sensitivity analyses will be conducted to explore key uncertainties. Where appropriate these will be combined with a stochastic analysis (e.g. bootstrapping) and probabilistic sensitivity analysis (economic model).

Data will be presented as point estimates and-cost effectiveness acceptability curves for the CUA and model based analysis and net benefit curves for the CBA.

## 10.4. Exploratory Analysis of Sustainability Factors

Each of the 4 interventions will be carbon-costed using an appropriate carbon-costing tool.

## 10.5. Interim Analyses and Criteria for the Premature Termination of the Trial

An Independent Data Monitoring Committee will review accumulating safety and efficacy data over the course of the trial, however no formal interim analyses are planned and there are no pre-defined stopping rules for safety, efficacy or futility.

The trial incorporates a pilot phase with progression criteria to assess the feasibility of recruitment. The pilot phase will involve six hospital sites and it is planned that these will open at a rate of two per month, to maximise recruitment.

**Progression criteria for pilot phase. Stop/Go criteria**

The first six months of recruitment will comprise the internal pilot feasibility phase. To deliver the 536-sample size in 20 months we would need an average recruitment rate of 3.2 men per site per month. Thus, we aim to recruit 18% of our participant target (96 patients) in the first six-month internal pilot (30 "site months") of the study; the remaining 82% of required participants will be recruited in the remaining 136 "site months" of the study. At the end of the six-month internal pilot we will regard recruitment of less than 48 participants as indicating that the trial is not feasible and, unless there are

compelling mitigating circumstances such as zero recruitment at some of the sites due to reasons beyond our control, consider the future of the trial, with our oversight committees, and with the funder. Recruitment of between 48 and 95 participants would trigger alterations to the recruitment plan; such as increasing the number of planned sites and possible extension to recruitment period. The extent of alterations will depend on how close the recruitment was to 96: recruitment of 78 (80% of target) or more participants would entail only minor finessing of the recruitment strategy. If any of these recruitment targets are not met, then an extra meeting of the TSC will be arranged in order to explore any common themes or barriers to recruitment. Recruitment strategies will be reviewed and revised throughout the trial to optimise recruitment.

| | Red | Amber | Green |
|---|---|---|---|
| **Trial recruitment** | <50% | 50-99% | ≥100% |
| **Recruitment rate/ site/ month** | <1.6 | 1.6-3.1 | ≥3.2 |
| **Total number of participants recruited** | <48 | 49-95 | ≥96 |
| **Number of sites opened** | ≤3 | 4-5 | ≥6 |

# 11. Data Handling

## 11.1. Data Collection Tools and Source Document Identification

Clinical data for all trial participants will be collected by the PI or their delegated nominees at site and during remote telephone visits. Data will be recorded in the eCRF of the trial's database (Sealed Envelope's Red Pill) and on relevant trial specific worksheets. As detailed in sections 7.6 and 7.7. operating surgeons will have the option of recording study data either onto trial specific worksheets, or directly into the Sealed Envelope's Red Pill database via the use of an electronic portal.

PROMs in the form of questionnaires will be completed directly by participants using Red Pill's ePRO or on paper which will be returned to the lead site research team for entry into the Red Pill database. Participant identification on the eCRFs and paper documentation will be through a unique participant number. A record linking the patient's name to the unique participant ID will be held within the ISF and is the responsibility of the PI. As such, patients cannot be identified from eCRFs.

As participants and operating surgeons have the option to complete their study data electronically (PROMs and Pre-Procedure Checklist and Operative Parameters respectively), Sealed Envelope's Red Pill may sometimes contain the actual source data. A downloadable copy can be available for the site.

The PI or nominated delegate will continually monitor completeness and quality of data in the eCRF and will correspond regularly with site staff with the aim of capturing all data and ensuring continuous high quality of data. A Source Data Agreement will be completed prior to the trial opening which will record what will be used as source data.

## 11.2. Data Handling and Record Keeping

The overall responsibility for data collection, quality and retention of trial data is with the Chief Investigator. Data will be handled, computerised and stored in accordance with the Data Protection Act 2018. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

## 11.3. Access to Data

Staff involved in the conduct of the trial, including the PIs, trial management team and NHS staff involved in screening, treatment and follow-up will have access to the ISF. The trial's data and participant medical records may be looked at by NCTU during monitoring and the Newcastle upon Tyne Hospitals NHS Foundation Trust during auditing

Secure pseudo-anonymised electronic data will be released to the trial statisticians and health economists for analysis. Postcode data will be used by the data manager to obtain the index of multiple deprivation score from the Office of National Statistics website (where available). Postcode data will not be shared or reported.

The NCTU trial management team will have access to the participants' names and contact details (including telephone number, email and postal address), which will be held securely within NCTU for the purposes of centrally administering the PROMs at the two and three year follow up visits and the sending of gift vouchers, as required.

The PI and trial site staff involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Password limited access to the trial database, restricted to delegated role will be granted to each site's PI and their delegated data entry and randomisation personnel at that site. NCTU trial management team will have access to the trial's database for monitoring purposes.

## 11.4. Archiving

All trial data will be stored for 5 years in accordance with UK GCP legislation and the Sponsor and NCTU SOPs.

# 12. MONITORING, AUDIT & INSPECTION

A trial monitoring plan will be developed, based upon the trial risk assessment, and agreed by the Trial Management Group, NCTU QA representative and the Sponsor.

All monitoring activity will be detailed in the monitoring plan. Monitoring of trial conduct and data collected will be performed by a combination of central review and off- and on-site monitoring visits to ensure the trial is conducted in accordance with GCP and appropriate regulations. Trial site monitoring will be undertaken by NCTU Trial personnel as indicated in the monitoring plan.

All monitoring findings will be reported and followed up with the appropriate personnel in a timely manner. Sites will be expected to assist the Sponsor in monitoring the trial e.g. hosting monitoring visits, providing information for on- and off-site monitoring and responding to monitoring findings within the timeframes requested, wherever possible.

The trial may be subject to audit by representatives of the Sponsor. Each investigator site will permit trial-related monitoring and audits including access to all essential and source data relating to the trial.

# 13. TRIAL OVERSIGHT

## 13.1. Data Monitoring Committee (DMC)

The DMC will consist of at least three independent members including an Independent Chair, an Independent Statistician and an Independent Clinician. The DMC will make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate changes to the trial, including the Stop/Go progression criteria that forms part of the pilot phase as per section 10.5 and review of accumulating safety data. The DMC will meet at the start of the trial, regularly throughout the recruitment and follow-up period of the trial, and on an ad hoc basis if required.

## 13.2. Trial Steering Committee (TSC)

The TSC will consist of at least three independent members including an Independent Chair, and Independent Statistician, Independent Clinician and lay members. The TSC will oversee and supervise the progress of the trial and ensure that it is being conducted in accordance with applicable guidance and regulations. It will provide advice on the trial design and discuss proposals for substantial protocol amendments where relevant, endorsing these as appropriate. The TSC will review recommendations from the DMC and provide advice regarding trial progress, to maximise the chances of completion within the proposed time scale. The TSC will meet following DMC meetings.

## 13.3. Trial Management Group (TMG)

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the day-to-day progress of the trial. The day-to-day management of the trial will be co-ordinated by Newcastle Clinical Trials Unit (NCTU). The Trial Management Group will include the CI, Senior Trial Manager, Trial

Manager, Statisticians, Sponsor Representative, Data Manager, Senior Project Manager, Co-Investigator(s), as appropriate.

Quality control will be maintained through adherence to NCTU and Sponsor Standard Operating Procedures (SOPs), the trial protocol, the principles of GCP, research governance framework

- The following functions falling under the responsibility of the Sponsor will be delegated to the Chief Investigator and supported by NCTU: Ethics Committee Opinion (including application for research ethics committee favourable opinion, notification of protocol amendments and end of trial, site specific assessment & local approval)
- HRA and Health and Care Research Wales (HCRW) Approval
- Good Clinical Practice and Trial Conduct (including Good Clinical Practice (GCP) arrangements, data monitoring, emergency & safety procedures).

# 14. ETHICAL AND REGULATORY CONSIDERATIONS

## 14.1. Research Ethics Committee Review and Reports

NCTU will obtain a favourable ethical opinion from an NHS Research Ethics Committee (REC) prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

NCTU will notify the REC of all required substantial amendments to the trial. Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or URSEs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

## 14.2. Peer Review

The study was peer reviewed by the NIHR HTA panel with expert reviews fed back to the investigators prior to funding approval.

## 14.3. Public and Patient Involvement

A patient group was set up at the lead site (Newcastle) including patients with direct experience of LUTS treatments and for treatments for retention of urine. They advised on several important aspects of trial design and patient facing materials. Members of the group have confirmed their willingness to continue review of study documentation intended for participants, advise on recruitment and be involved in the trial all the way through to dissemination of results. The PREMISE PPI group is now

independent from the lead site and includes members from across the UK. If required by the group, one of the members will act as chair and communicate with the TMG on behalf of the group. In addition, other PPI members will be invited to sit on the Trial Steering Committee to ensure patient input at all stages, from early design through to publication and dissemination of results.

## 14.4. Regulatory Compliance

The trial will be conducted in accordance with the Research Governance Framework. Before any site can enrol patients into the trial, that site must have issued confirmation of capacity and capability (England/Wales) or local approval (Scotland).

## 14.5. Protocol Compliance

It is the responsibility of the CI to ensure that the clinical investigation is run in accordance with GCP and the protocol. Study tasks may be delegated to a suitably qualified or experienced member of the research team but the CI and PI will retain overall responsibility for adherence to protocol and GCP. The trial will be monitored by NCTU staff, to measure protocol compliance and manage deviations. Site staff are responsible for compliance with the protocol in their everyday trial activities, and must report anything that they feel constitutes a protocol deviation, serious breach, anything that requires an USM, or anything else that should be reported and documented between monitoring visits.
Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Deviations from the protocol and GCP occur in clinical trials and the majority of these events are technical deviations that are not serious breaches. These events must be documented on the protocol deviation log, including the relevant Corrective and Preventive Actions (CAPA) required. Protocol violations are a consistent variation in practice from the study protocol or deviations that could potentially impact on study participant's rights/safety or affect the scientific value or outcome of a study. The PI will sign off each deviation and decide whether this is a deviation or violation. Violation documentation must be completed within three days of the violation being discovered using the violation reporting form.

Deviations or violations that are found to frequently recur at a site are not acceptable and could be classified as a serious breach.

## 14.6. Notification of Serious Breaches to GCP and/or the Protocol

A serious breach is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial

The sponsor must be notified immediately of any incident that may be classified as a serious breach and will determine whether the incident qualifies as a serious breach. The NCTU will notify the NHS REC within the required timelines in accordance with the NCTU SOP based on the Sponsor decision.

## 14.7. Data Protection and Patient Confidentiality

The trial will be run in accordance with the Data Protection Act 2018, to maintain the confidentially of trial participants and trial data integrity.

Overall responsibility for data collection lies with the Chief Investigator. Data will be handled, computerised and stored in accordance with the Data Protection Act 2018. The overall quality and retention of trial data is the responsibility of the Chief Investigator. All trial data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

All investigators and trial site staff must comply with the requirements of the applicable legislation with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the legislation. Explicit consent must be obtained via the informed consent form from each trial participant to allow data sharing to occur.

Personal data will be regarded as strictly confidential. All trial files will be securely stored and access restricted to staff involved in the trial. Research staff at sites will enter data onto a secure web-based electronic database (Red Pill, Sealed Envelope) maintained by the NCTU. Data will be entered using unique participant trial numbers. Access to this database will be password protected and limited to staff at research sites or those employed by Newcastle University who are involved in the trial.

## 14.8. Indemnity

The Sponsor will provide indemnity in the event that trial participants suffer negligent harm due to the management of the trial provided under the NHS indemnity arrangements for clinical negligence claims in the NHS.

The substantial employers of the protocol authors will provide indemnity in the event that trial participants suffer negligent harm due to the design of the trial.

The trial sites will provide indemnity in the event that trial participants suffer negligent harm due to the conduct of the trial at their site. For NHS Organisations this indemnity will be provided under the NHS indemnity arrangements for clinical negligence claims in the NHS. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements. Trial staff without NHS contracts e.g. General Practitioners or Dentists will provide their own professional indemnity.

## 14.9. Amendments

It is the responsibility of the Research Sponsor to determine if an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and the Trial Management Group. The TSC will be made aware of all substantial protocol amendments.

Substantial amendments will be submitted to the REC and will not be implemented until this approval is in place. It is the responsibility of NCTU on behalf of Sponsor to submit substantial amendments.

Non-substantial amendments will be submitted to the HRA/HCRW and will not be implemented until authorisation is received (if applicable).

Substantial amendments and those non-substantial amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by the NCTU.

### 14.10. Access to the Final Trial Dataset

Until publication of the trial results, access to the full dataset will be restricted to the Trial Management Group and to authors of the publication.

Anonymised/pseudonymised data from this trial/study may be available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the lead author/Chief Investigator and NCTU in line with any applicable data sharing policies.

# 15. DISSEMINATION POLICY

The landscape of interventional treatments for the LUTS BPE is rapidly changing with many new, minimally invasive treatments being available. This RCT, for the first time, will provide a sound outcome data comparing most common MITS against a long-established invasive treatment (TURP). The results would benefit all the stakeholders involved in the trial. We expect many outputs from the study: Conference presentations of the results in the poster and podium formats (In National and International annual meetings, as well as other specialty meetings). A comprehensive publication strategy of scientific papers in the peer reviewed journals will ensure the main outcomes and additional analyses are reported. Data may be published at multiple timepoints during the duration of the study. As well as dedicated public websites displaying the results of the trial all participants and the PPI will be informed of the trial findings by letter if they so wish. Making results available to various local/national and international guidelines committees e.g. NICE, LUTS BPE guidelines panels is a priority as well as a willingness to share trial data with appropriate other bodies and researchers. The results would also be useful to the regional task forces and guideline panels, in deciding how best to adopt and set up new loco-regional services taking into account resources and patient needs (e.g. National Planned Care Programme - Benign prostatic hyperplasia: Task and Finish Group, Wales).

**Device manufacturers**: This study would help manufacturers gain valuable information about product performance in an RCT setting. It could help them look at the advantages and disadvantages of the technology and devices as well as identify subgroups of patients where the treatments might work better or fail. This could further bring in improvements to the technology. It would also help them get regulatory approvals. At the local level, individual trusts and health boards can look at the clinical and health economic outputs of the study to focus on rational resource allocations, while balancing the needs of patients and providers. The study methodology and proforma could offer a framework for ongoing evaluation of the adopted technologies at the loco-regional (e.g. service evaluation audits) or national audits e.g. BAUS Urology Audits. The study is expected to provide results that would help

clinicians in evidence-based patient counselling and informed decision making in their daily clinical practice.

**Informing and engaging patients and the NHS:** We will have a multistep approach in informing and engaging patients and wider population as well NHS authorities. This would involve: Presentations and publications of the results in the Urological, healthcare safety and policy settings, as well as health economic forums, conferences and journals. –This would help disseminate the results in the scientific as well as associated media and social platforms. We will publicise the results on the sponsor NHS trust, NCTU and Imperial College websites. We will actively communicate with the NICE technology appraisals and updates teams. We would publicise the results on the dedicated public website(s). The results would be made available to manufacturers and used in their websites and public communication portals. We will explore additional help from the NIHR communications team as well as interested Media and Press in publication of the results (considering existing high level of press interest in these technologies).

**Delivering the output within healthcare:** We anticipate different routes for the results to enter into the healthcare system as well as society in general. Publications of the conference proceedings as well as scientific papers. Feedback of the results to the PAGs, clinicians. Use of dedicated public websites and trust net sites that offer patient information. Manufacturers' websites, training tools as well as press releases and communication portals publication by the interested social media platforms and press. Dissemination of the results with the help of national and international Urology associations will drive the impact of the study into real practice change.

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# 16. APPENDICES

## 16.1. Appendix 1 – Amendment History

| **Amendment: NA01** | **Protocol version: 3.0** | **Author(s) of changes: TMG** |
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| Summary of changes:<br>• 6.2. Exclusion criterion wording around PSA has been updated from: 'Any known or suspected prostate cancer treated or untreated; (if known) PSA ≥ 0.15' to 'Any known or suspected prostate cancer treated or untreated; (If PSA has been performed outside of trial investigations PSA density ≥0.15 would be an exclusion unless prostate cancer has been excluded)<br>• 9.3.3. Assessment of Expectedness table has been reformatted and expected events for each procedure are now in alphabetical order. Duplicated event of 'urinary retention' has been removed from the TURP section<br>• 11.1 Clarification has been added to state that where Sealed Envelope's Red Pill may sometime contain source data, a downloadable copy can be available for the site<br>• Other minor typographical changes and reformatting throughout and clarifications to Sections 7.13, 9.3.1 and 9.4.<br>• Safety Reporting diagram has been updated to be consistent with protocol text | | |
| **Amendment: NA04** | **Protocol version: 4.0** | **Author(s) of changes: TMG** |
| Summary of changes:<br>• 6.1. Inclusion Criteria, clarification has been added to state that prostate volume up to and including 80ml ($cm^3$) is eligible<br>• 7.1.1. Patient Identification, clarification that although potentially eligible patients will be identified and approached by a member of the direct care team, they will not hand out a copy of the PIS to the patient<br>• 7.1.2. Consent, has been updated to state that informed consent for the trial can be taken by a delegated member of the research team (in agreement with local site policies), who is appropriately trained and delegated to do so<br>• 7.1.3. Screening and Eligibility Assessment, 7.6.3. Digital Rectal Exam and 7.13. Schedule of Events have been updated to state that a DRE is required at screening where cancer has not previously been excluded by either DRE, or MRI, or a negative biopsy within 12 months prior to consent<br>• 7.1.3. Screening and Eligibility Assessment and 7.6.2. Prostate Volume have been clarified to state that where a patient has previously had 2 or more volume assessments by different | | |

measurements within the 12 months set period, the clinician can use their discretion as to the most appropriate modality to use. Any concerns about eligibility can be discussed with the CI.

- 7.7. Pre-Procedure Checklist has been clarified to state that any concerns about continuing eligibility can be discussed with the CI.

- 8.1. Training and Competence, has been updated to reduce the required pre-requisite cases forming part of the mandated training pathway for Prostatic Urethral Lift and Rezum from 20 to 10 cases

- 8.1. Training and Competence, has been updated to state that a surgeon in training may perform the procedure or part of it, provided that they are under the direct supervision of a surgeon who has completed the mandated training pathway and who has been appropriately delegated the task of performing the procedure by the PI (as documented via the delegation log).

| **Amendment: NA07** | **Protocol version: 5.0** | **Author(s) of changes: TMG** |
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Summary of changes:

- Trial Summary section addition of a footnote to explain if recruitment to the trial is lower than anticipated, consideration will be made to the addition of further research sites.

- 5.0 'study setting', added PIC wording where participants will also be identified through local neighbouring trusts acting as participant identification centres (PICs).

- 7.1.1 'Patient Identification', added PIC wording for potential participants identified at PIC sites and notifying the trial site. Added the use of the trial poster to inform potential participants of the trial and advise to discuss potential participation with their local direct care team during routine clinical visits.

- 7.1.2 'Consent' added text (and referring PIC where applicable).

- 7.6.4 'Flow Test and Post Void Residual' made a clarification to text regarding when test can be completed and removed the requirement for the test to be completed by a delegated trial person and 7.13. 'Schedule of Events' updated accordingly

- 7.16 'Post trial Care' added where a participant has been referred from a PIC site, they may remain under the care of the team at the research site hospital trust for standard care.

| **Amendment: SA15** | **Protocol version 6.0** | **Author(s) of changes: TMG** |
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Summary of changes:

- 2. 'Rationale', additional information on PPIE input on trial design added

- 3. 'Objectives and Outcome Measures', additional secondary objective added; 'To compare the surgical re-intervention rate'

- The following sections have been updated to reflect the change in the trial design to allow patients to choose at least two of the four trial interventions to be randomised between (11 possible randomisation schemes); 4. 'Trial Design', 7.1.2. 'Consent', '7.1.3. 'Screening,

Randomisation Choice and Eligibility Assessment', 7.2. 'Randomisation', 7.2.2. 'Randomising a participant', 8. 'Trial Intervention'

- 5. 'Study Setting', reference to using established urology area networks, the provision of training sites in MITS and reference to the pilot phase removed.
- 6.1. 'Inclusion Criteria', text added to specify a minimum prostate size of 30ml ($cm^3$).
- 6.2. 'Exclusion Criteria', text added to clarify exclusion for catheter dependent self catheterising patients and patients actively participating in another interventional urological trial which may impact the outcomes of the PREMISE trial and reference to 1.3. 'Co-enrolment' section.
- 6.3. 'Co-enrolment' section added to clarify that co-enrolment of PREMISE participants to other current trials must be checked and agreed with the Chief Investigator.
- 7.1. 'Patient Identification', removal of reference to urology area networks and addition of text regarding the use of a patient recruitment and patient experience videos via the trial website.
- 7.3. 'Post-Intervention Participant Diary', text added to include addition of details of surgical re-intervention required for urological symptoms.
- 7.4. 'Participant Pathway', text added regarding possible central administration of PROMs and sending of gift vouchers by NCTU.
- 7.5.4. 'Flow Test and Post Void Residual', text added to clarify when a screening/baseline test is required and clarification that participants unable to produce a voided volume of >125ml may still be eligible for the trial.
- 7.5.5.6 'Randomisation treatment choice' added regarding additional question on reasons for randomisation treatment choices to be added to the PROMs at the six week visit.
- 7.5.5.10 'Re-intervention Status (Additional surgical procedures)' added regarding additional question on subsequent need for surgical re-intervention to be added to PROMs.
- 7.7. 'Operative, Perioperative and Post-operative Parameters', text added regarding collection of data on surgical re-intervention.
- The following subsections have been updated in 9. 'Safety Reporting' to reflect that due to the safety profile of the four interventions being well-established, only unexpected SAEs related to the intervention (URSEs) will require expedited safety reporting and all adverse events will be recorded in the database, assessed for severity as per the Clavien Dindo criteria and reviewed by the DMC on a regular basis; 9.2.1. 'Recording of Adverse Events', 9.3 'Expedited Safety Reporting', 9.3.1 'Reporting SAEs', 9.3.2. 'Exclusions to SAE Reporting'.
- 9.3.3. 'Assessment of Expectedness', additional events added and text updated to state that both PI and CI will perform expectedness assessment.
- 9.8. 'Responsibilities', updated to include Principal Investigator responsibility to perform assessment of expectedness of all intervention-related SAEs.
- 10.1. 'Analysis Populations', new 'As-treated' analysis population defined.
- 10.2. 'Sample Size Calculations', detail added on which randomisation schemes will be pooled for analysis. Inclusion of statement that over-recruitment may be required to obtain a sufficient number of participants evaluable for each comparison, low recruiting arms may be terminated, and historical control data may be utilised.

- 10.3.1. ‘Analysis of the Primary Outcome Measure,’ included that IPW will be used if the proportion of eligible participants not undergoing their allocated treatment is >5%. Sensitivity analyses related to this have also been added. This reflects the additional detail provided in the Statistical Analysis Plan and emerging literature on the topic of estimands for non-inferiority trials which was not available when the original protocol was written. Additional sensitivity analyses added which will pool data across all randomisation schemes. CACE analyses defined as supplementary rather than sensitivity analyses. Analyses in ‘as-treated’ population included as supplementary analyses.
- 10.3.2 ‘Analysis of the Secondary Outcome Measures’ detail added on which randomisation schemes will be pooled for analysis. Analysis population to be used for secondary outcomes amended from modified ITT to per-protocol as this aims to answer a more relevant clinical question in this setting. Inclusion of analysis methods for new secondary outcome of re-intervention rates.
- 10.3.5. ‘Health Economics Analysis’ text added that historical control data may be utilised.
- 11.3. ‘Access to Data’, detail added that the NCTU management team will have access to and securely hold participants’ names and contact details for the purposes of centrally administering PROMs and gift vouchers.