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:	v2.0 29 March 2023

Statement:

This protocol has regard for the HRA guidance.

RESEARCH REFERENCE NUMBERS

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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

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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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Senior Statistician

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Newcastle Clinical Trials Unit Representative

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Position:

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PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: PREMISE Trial

Principal Investigator

I have carefully read and understood protocol version 2.0. I agree to conduct the trial in compliance with Good Clinical Practice.

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TRIAL SUMMARY

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** Prostate Resection versus Minimally Invasive Surgery Evaluation Trial	
Summary of Trial Design	Multi-arm, multi-centre, non-inferiority 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 up to 80ml, who are offered surgery for bladder outlet obstruction (BOO) within an NHS setting.	
Intervention	Prostatic urethral lift (PUL) vs Temporary Implantable Nitinol Device (iTIND) vs Water vapour ablation (Rezum) vs TURP (Control)	
Planned Sample Size	536	
Planned Number of Sites	10	
Intervention Duration	Single procedure treatment	
Follow Up Duration	three years	
Planned Trial Period	71 months	
	Objectives	**Outcome Measures**
Primary	To compare the clinical effectiveness of three 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

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 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 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: • Post void residual • Maximum flow rate (Qmax)
	To compare incidence of adverse events	Adverse events up to six months post-intervention collected via: • Operative parameters • 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 • ICIQ-LUTSqol at baseline, six months, 12 months, two and three years post-intervention • EQ-5D-5L at baseline, six weeks post-intervention, six

		months, 12 months, two and three years post-intervention
	To establish the most suitable outcome measure for the context of male LUTS intervention	Correlation of I-PSS / ICIQ-MLUTS
	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 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
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 Utility scores derived from responses to the EQ-5D-5L questionnaire at baseline, six weeks post-intervention, six and 12 months post-intervention

		Average QALYs per participant at 12 months post-intervention
	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 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 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

Contents

GLOSSARY OF ABREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AR	Adverse Reaction
ARSAC	Administration of Radioactive Substances Advisory Committee
BOO	Bladder Outlet Obstruction
BPE	Benign Prostate Enlargement
CEA	Cost-Effectiveness Acceptability
CEAC	Cost-Effectiveness Acceptability Curves
CI	Chief Investigator
CNS	Central Nervous System
CRF	Case Report Form
IDMC	Independent Data Monitoring Committee
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Human Tissue Authority
HTAct	Human Tissue Act
IC	Intermediate Care
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
IRMER	Ionising Radiation (Medical Exposure) Regulations
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
iTIND	Temporary Implantable Nitinol Device
LCRN	Local Clinical Research Network
MITS	Minimally Invasive Treatment
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
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
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
USAR	Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trials Steering Committee
TURP	Transurethral Resection of Prostate
UAN	Urology area network

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.

The trial design was developed with input from patient representatives on several important areas and their guidance was followed on randomisation (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
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 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 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: • Post void residual • Maximum flow rate (Qmax)
	To compare incidence of adverse events	Adverse events up to six months post-intervention collected via: • Operative parameters • 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 • ICIQ-LUTSqol at baseline, six months, 12 months, two and three years post-intervention • 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
	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
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

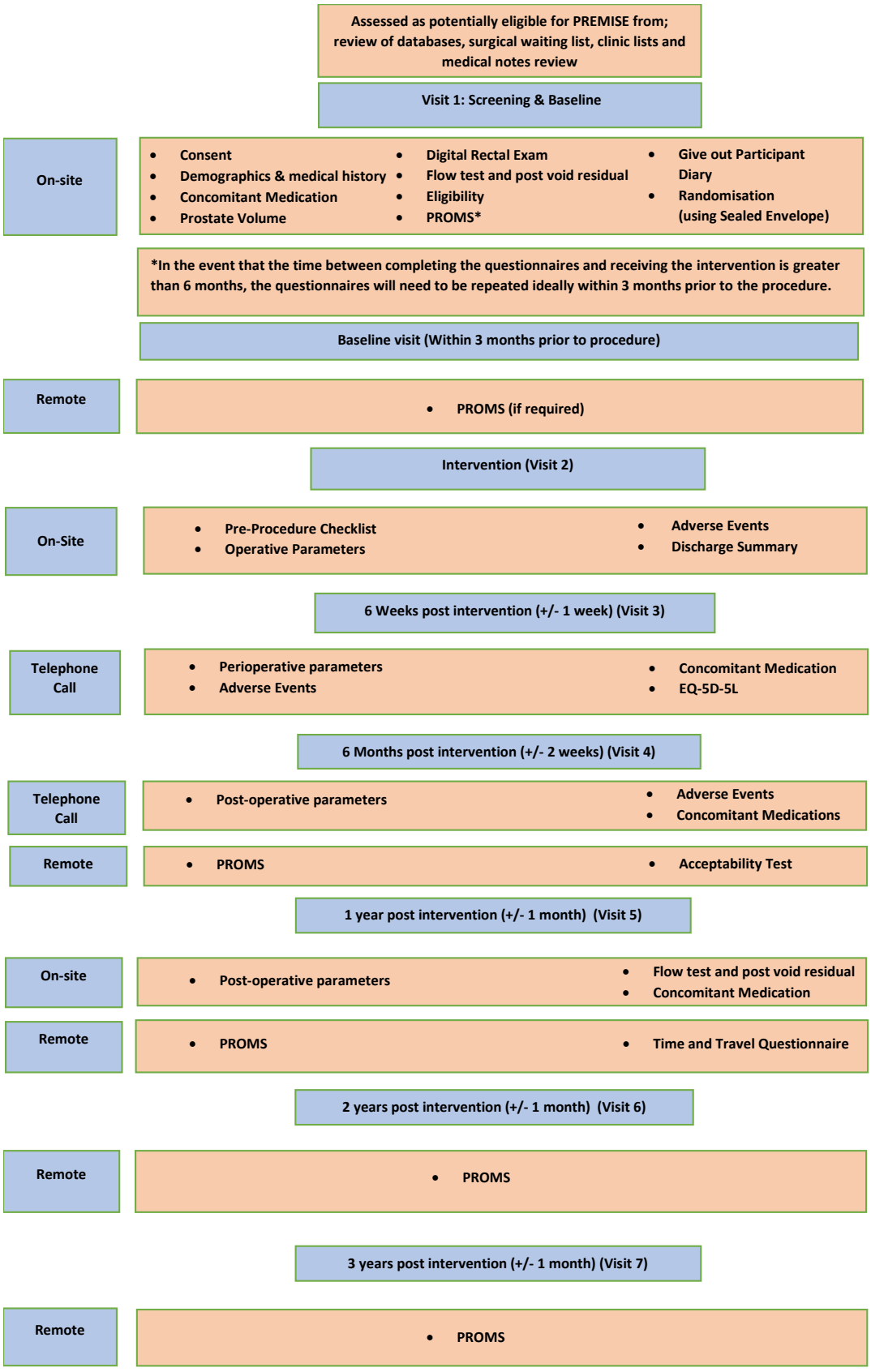
		Utility scores derived from responses to the EQ-5D-5L questionnaire at baseline, six weeks post-intervention, six months and 12 months post-intervention Average QALYs per participant at 12 months post-intervention
	To compare the cost effectiveness of the interventions at two years and three years post-intervention	Incremental cost per quality-adjusted life year (QALY) gained at two and three years post-intervention 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 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, randomised controlled trial with a six-month internal pilot with defined progression criteria. In total, 536 participants will be recruited and followed up for three years post-intervention. Eligible participants will be randomised 1:1:1:1 to TURP, PUL, Rezum and iTIND.

All sites will offer all interventions. In some sites this may be as part of a Urology area network (UAN). A UAN 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 within their functioning UAN. A designated lead research site within the UAN 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.

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. After recruitment, treatment will be delivered by a consultant 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.).

In sites that only offer their population limited choice in treatment options for LUTS, specific training in the new MITS will be provided to allow these sites to open after the pilot phase. Using established urology area networks will allow standardization of surgeon experience and avoid the need for travel costs associated with patient travel to distant sites for inclusion in the trial.

6. ELIGIBILITY CRITERIA

6.1. Inclusion Criteria

1. Men aged 50 years or over
2. Prostate volume up to 80ml (cm^3) (measured by ultrasound or cross-sectional scan)
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 known) PSA ≥0.15
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 self catheterising
6. Predicted life expectancy less than three years
7. Participation in any other current interventional trial

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.

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. We will use established Local Clinical Research Network (LCRN) links to ensure that colleagues within each Urology area network (UAN) are aware of the trial and can direct referrals accordingly. 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 and given a copy of the PIS. 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.

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 any 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 the PI or by a research nurse (if 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 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 and Eligibility Assessment

Following consent and 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 by transrectal ultrasound (where prostate volume is not available for current episode of urinary symptoms from medical records within 12 months prior to consent e.g. by previous transrectal ultrasound or via existing cross-sectional scan)
- Digital Rectal Exam to exclude cancer (where this has not previously been performed within 12 months prior to consent)

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

Permuted random blocks of variable length will be used to allocate participants 1:1:1:1 to control (TURP) or one of the 3 MITS. Stratification will be by 1) Urology Area Network; 2) whether or not the participant is taking anti-platelet and/or anticoagulant drugs pre-operatively; 3) whether or not the participant has diabetes (includes type 1 and 2).

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: https://www.sealedenvelope.com/access/ 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.

Once consent is obtained and eligibility confirmed, the research team should access the randomisation system, which should allocate the patient to receive one of the four procedures. The allocation should be documented in the participant medical records and the patient should be informed of their randomised treatment.

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

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

7.4. Blinding

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.

The trial statistician and senior trial statistician will be unblinded for the purposes of producing and reviewing reports to the Independent Data Monitoring Committee (IDMC). Unblinded reports will be kept confidential and will only be viewed by the IDMC 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.

7.5. 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 designated Urology Area Network. 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 Urology Area Network (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 12 months visit and the administration and data entry of patient reported outcome measure (PROM)s (where these are to be completed on paper), as well as sending out gift vouchers following completion of questionnaires at two and three years. 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.

7.6. Trial Assessments

7.6.1. 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

7.6.2. 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.

7.6.3. Digital Rectal Exam

Where a digital rectal exam has not been performed as standard care within 12 months prior to consent, this will be performed at the screening visit by a delegated member of the trial team in order to exclude cancer.

7.6.4. 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, this will be completed by a delegated member of the trial team at the screening visit (once eligibility has been confirmed).

7.6.5. 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 or text message, 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 & 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.

7.6.5.1. 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.

7.6.5.2. 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’.

7.6.5.3. 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'.

7.6.5.4. 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'.

7.6.5.5. 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.

7.6.5.6. 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.

7.6.5.7. 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.

7.6.5.8. 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?'

7.6.5.9. 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.

7.6.5.10 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.

7.6.5.11 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.

7.7. 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.

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).

7.8. 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.

As described above in section 7.5.6. surgeons will have the option of either completing a trial specific paper form or entering the data electronically. 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 7.5.6., 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

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

7.9. 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.

7.10. 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.

7.11. 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.

7.12. 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.

7.13. Schedule of Events

	Screening	**Baseline (within 3 months prior to procedure)**	**Intervention**	**6 weeks post-intervention** (+/-1 week)	**6 months post-intervention** (+/-2 weeks)	**12 months post-intervention** (+/- 1 month)	**2 years post-intervention** (+/- 1 month)	**3 years post-intervention** (+/- 1 month)
Type	**On-site**	**Remote**	**On-site**	**Remote + Telephone Call**	**Remote + Telephone Call**	**Remote + On-site**	**Remote**	**Remote**
Consent (must be done prior to any assessments)	**X**							
Demographics and Medical History	**X**							
Prostate Volume	**X**[b]							
Digital Rectal Exam	**X**[c]							
Eligibility	**X**							
Randomisation	**X**							
Give out Post-Intervention Participant Diary	**X**							
Flow Test and Post Void Residual	**X**[d]					**X**		
Pre-Procedure Checklist			**X**					
Operative Parameters			**X**[e]					
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)	Intervention	6 weeks post-intervention (+/-1 week)	6 months post-intervention (+/-2 weeks)	12 months post-intervention (+/- 1 month)	2 years post-intervention (+/- 1 month)	3 years post-intervention (+/- 1 month)
Type	**On-site**	**Remote**	**On-site**	**Remote + Telephone Call**	**Remote + Telephone Call**	**Remote + On-site**	**Remote**	**Remote**
Patient Reported Outcomes[f]								
Post-intervention catheterisation status					X[g]	X[g]	X[g]	X[g]
Hospitalisation Attendance Questionnaire					X	X		
Catheterisation Questionnaire							X	X
I-PSS inc Qol	X[a]	X[a]			X	X	X	X
EQ-5D-5L	X[a]	X[a]		X	X	X	X	X
ICIQ-MLUTS	X[a]	X[a]			X	X	X	X
ICIQ-MLUTSsex	X[a]	X[a]			X	X	X	X
ICIQ-LUTSqol	X[a]	X[a]			X	X	X	X
Healthcare Services	X[a]	X[a]			X	X	X	X
Time and Travel						X		
Acceptability Test					X			

[a] 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.

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

[c]Where assessment data is not available from standard of care within 12 months prior to consent

[d]Where no assessment data is not available from standard care within 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 if more convenient.

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

[f]Paper/electronic response

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

7.14. 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.

7.14.1. 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.

7.14.2. Discontinuation criteria

If a randomized 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 randomized intervention. This would not be considered a withdrawal of consent but would be regarded as a discontinuation of their allocated intervention.

If a randomized 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 local site/UAN. 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.

7.15. End of Trial

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

7.16. Post Trial Care

At the end of their participation in the study participants will continue to receive standard NHS care.

8. TRIAL INTERVENTION

Participants will be randomised to one of four interventions:

I. Prostatic urethral lift (PUL)

II. Rezum

III. Temporary Implantable Nitinol Device (iTIND)

IV. TURP

Please see section 2. Rationale. All sites will offer all four trial interventions with some sites forming part of a Urology area network (UAN), where patients may receive their designated treatment within their locality, but away from their originating hospital or trust.

8.1. Training and Competence

All participating surgeons will have completed a mandated training pathway, including more than 20 cases for PUL and Rezum, and five cases for iTIND since completing training. Additionally, we will record the total number of cases performed by each surgeon for each MITS in their career as well as the year preceding starting the study 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.

8.2. Known Risks

Please see Assessment of Expectedness in section 9.3.1 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: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • is otherwise considered medically significant by the investigator * - 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.

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 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 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

Grade	Definition
IV Life threatening complication (including CNS complications)* requiring IC/ICU management:	
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 to the intervention
No	The event is not considered related to the intervention
Unable to Determine	After review of the information the PI/delegated clinician is unable to determine if the event is related to the intervention or not

9.3. Safety Reporting

9.3.1. Reporting SAEs

Where an AE is assessed as serious, as well as recording in the participant's medical notes and the trial database eCRF as described above, it must also be reported as an SAE. If a participant withdraws from the study due to an SAE, the trial team will continue to follow up the event until the SAE has resolved or stabilised. SAEs must be reported within 24 hours of research staff becoming aware of the event.

9.3.2. Exclusions to SAE reporting

Events that are excluded from reporting as an AE for the study should not be reported as SAEs i.e. SAEs not related to the condition or the intervention do not require reporting, including death (see section 9.5)**.** In addition, planned hospital admissions for the study intervention are excluded from safety reporting.

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 SAEs will be allocated a unique SAE number and a confirmation of receipt returned to the sender. SAEs will be recorded by trial management personnel on the trial's safety database.

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 SAE 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 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 SAEs will be followed up until resolution, or until the participant reaches the end of the study. An SAE 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 will undergo documented review by the CI for each SAE.

9.3.3. Assessment of Expectedness

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

TURP	**Rezum**
Penile pain	Dysuria
Bladder/ abdominal pain	Urinary frequency
Passage of debris in urine	Haematuria
Passing of clots in urine	Hematospermia
Dysuria	Pain or discomfort in the pelvic area
Hemorrhage	Penile pain
Haematuria	Urinary tract infection
Urinary frequency	Sediment / debris in urine
Retrograde ejaculation	Retrograde ejaculation
Erectile dysfunction	Erectile dysfunction
Urinary retention	Urinary urgency
Urinary incontinence	Passing of clots
Stress incontinence	Urinary incontinence
Injury to the urethra	Urinary retention
Urinary tract infection	Urethral stricture
TUR-syndrome	Urinary leakage/ incontinence
Clot retention	Prostate abscess
Urosepsis	Return to theatre for resection of prostate
Urethral stricture	
Bladder neck stenosis	
Capsular perforation	
Bladder perforation	
Retained fragments	
Return to theatre for bladder wash out for bleeding	
Urinary retention	
iTIND	**PUL**
Pyrexia	Dysuria
Hemorrhage	Haematuria
Dysuria	Pain or discomfort in the pelvic area
Urinary tract infection	Urinary urgency
Local irritation	Temporary urinary urge incontinence
Urinary hesitancy	Urinary retention
Urinary frequency	Urinary tract infection
Urinary retention	Implant encrustation
Haematuria	Retrograde ejaculation
Hematospermia	Erectile dysfunction
Urinary incontinence	Penile pain
Bladder perforation	Passage of clots/ debris
Urethral stricture	Urethral stricture

Bladder neck stricture Changes to erectile function Retrograde ejaculation Pelvic discomfort Irritation to the meatus Inflammation to the prostatic urethra Inflammation to the bladder neck Pain or pressure in the perineal area Urinary urgency Penile pain Urinary leakage / incontinence Return to theatre for wash out / bleeding	Pelvic haematoma Urinary leakage / incontinence Return to theatre for wash out / bleeding
Anesthesia associated events	
Allergic reaction Chest infection Pulmonary embolus Stroke Deep Vein Thrombosis Heart Attack Death Nausea & Vomiting Drug reaction Aspiration Local inflammation / skin reactions / cellulitis Pain and conscious awareness Spinal haematoma Paralysis Nerve injury Sore throat and hoarse voice	

9.4. Recording and Reporting URSEs

All URSEs (related serious adverse events classed as unexpected according to the protocol section 9.3) 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 and date of birth

- Name of intervention
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g., Principal Investigator)

To ensure adherence with the required reporting timeframes, sites must notify NCTU of suspected URSEs immediately but no later than 24 hours after becoming aware. Information should be submitted on an SAE report form via secure e-mail to nctu.premise.sae1@nhs.net. 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. 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 (meeting the AE criteria described in section 9.2.1.) that result in death will meet the criteria for seriousness as defined in section 9.1. and will be reported accordingly as SAEs. Deaths for reasons that do not meet the criteria to be recorded as an AE (as described in 9.2.2.) will not meet the criteria for safety reporting (these events will still be recorded in the eCRF via the Death CRF).

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.
- Ensuring that all SAEs, including 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.
- Provide review of assessment of causality of all SAEs on behalf of Sponsor (where the assessment was not originally performed by the CI).
- Perform assessment of expectedness of all related SAEs on behalf of Sponsor.
- Immediate review of all USREs.
- 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 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 ratio throughout the life of the trial (may be delegated to NCTU).

TSC/IDMC

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

10. STATISTICAL CONSIDERATIONS

10.1. Analysis Populations

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

Analysis Population	Description
Intention-to-treat	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.
Safety	Includes all randomised participants receiving a trial intervention, analysed according to the intervention received.

For efficacy analyses, 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. 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). The trial is powered to test the non-inferiority (NI) of each experimental arm to the TURP arm in terms of I-PSS. 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 arm (400 in total) 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 536. Since we are adjusting for baseline I-PSS, we would expect power to be higher than 90%.

10.3. Statistical Analyses

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.

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 MITS compared to TURP in the subgroup of patients who 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	• Not undergoing randomised treatment – principal strata[1]
Population-level summary measure	Mean difference in I-PSS score at 12 months (adjusted for baseline) between each MITS and TURP

[1]*This principal strata strategy targets the treatment effect within the subgroup of patients who would have adhered to their allocated treatment*

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, variables used to stratify the randomisation, and a treatment-by-time interaction term. Random effects for Urology Area Network and individual (nested within UAN) will be used. 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

Estimates of the treatment effect in the per-protocol population may be biased if deviating from allocated treatment is related to randomised treatment group, or where patient characteristics that predict non-adherence also influence the outcome. As a sensitivity analysis we will also estimate the Complier Average Causal Effect (CACE), targeting the same estimand as described above, using Instrumental Variable (IV) methods.

Supplementary analyses

A supplementary analysis will estimate the mean difference in the change in the I-PSS symptom score from baseline to 12 months between those allocated to receive MITS compared to TURP, regardless of adherence to their randomised treatment allocation.

This supplementary estimand is described by the following attributes:

Estimand attribute	Description
Population	Patients offered surgery for BOO and meeting the PREMISE eligibility criteria
Treatment conditions	Allocation to 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	• Not undergoing randomised treatment – treatment policy[1]
Population-level summary measure	Mean difference in I-PSS score at 12 months (adjusted for baseline) between each MITS and TURP

[1]*This treatment policy strategy targets the treatment effect regardless of whether or not participants adhered to their allocated intervention*

These analyses will be carried out using a linear mixed-effects model as described above but performed in the modified intention-to-treat, rather than per-protocol, population. Analyses may also be repeated using the strict intention-to-treat population.

10.3.2. Analysis of the Secondary Outcome Measures

Secondary efficacy outcomes will be analysed for superiority of each experimental treatment against control in the modified ITT population, i.e. following a treatment policy approach. Estimated differences between treatment groups will be reported with 95% confidence intervals and two-sided p-values. 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 UAN as a random effect and treatment group, other stratification factors, 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 UAN 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 UAN as a random effect and treatment group and other stratification factors 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 UAN as a random effect and treatment group and other stratification factors as fixed effects.

The proportion of participants requiring a readmission, experiencing acute urinary retention, or requiring a catheter during follow-up will be analysed using mixed-effects logistic regression models, including UAN as a random effect and treatment group and other stratification factors as fixed effects. Time to readmission, catheterisation or acute urinary retention 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 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.

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 7.5.6. and 7.5.7 operating surgeons will have the option of recording study data either onto trial specific worksheets, or directly into the Sealed Envelope 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.

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 web site (where available). Postcode data will not be shared or reported.

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. Independent Data Monitoring Committee (IDMC)

The DMC will consist of at least three independent members including an Independent Chair, an Independent Statistician and an Independent Clinician. The IDMC 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 10.6. The IDMC 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 IDMC and provide advice regarding trial progress, to maximise the chances of completion within the proposed time scale. The TSC will meet following IDMC 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 USARs 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 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. Members of the group have confirmed their willingness to review study documentation intended for participants 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, one of the members will chair the group and communicate with the TMG on behalf of the group. In addition, 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 an AE, SAE, URSE, protocol deviation, serious breach, anything that requires an USM, or anything else that should be reported and documented between monitoring visits.

Protocol deviations, violations, non-compliances or breaches are departures from the approved protocol. 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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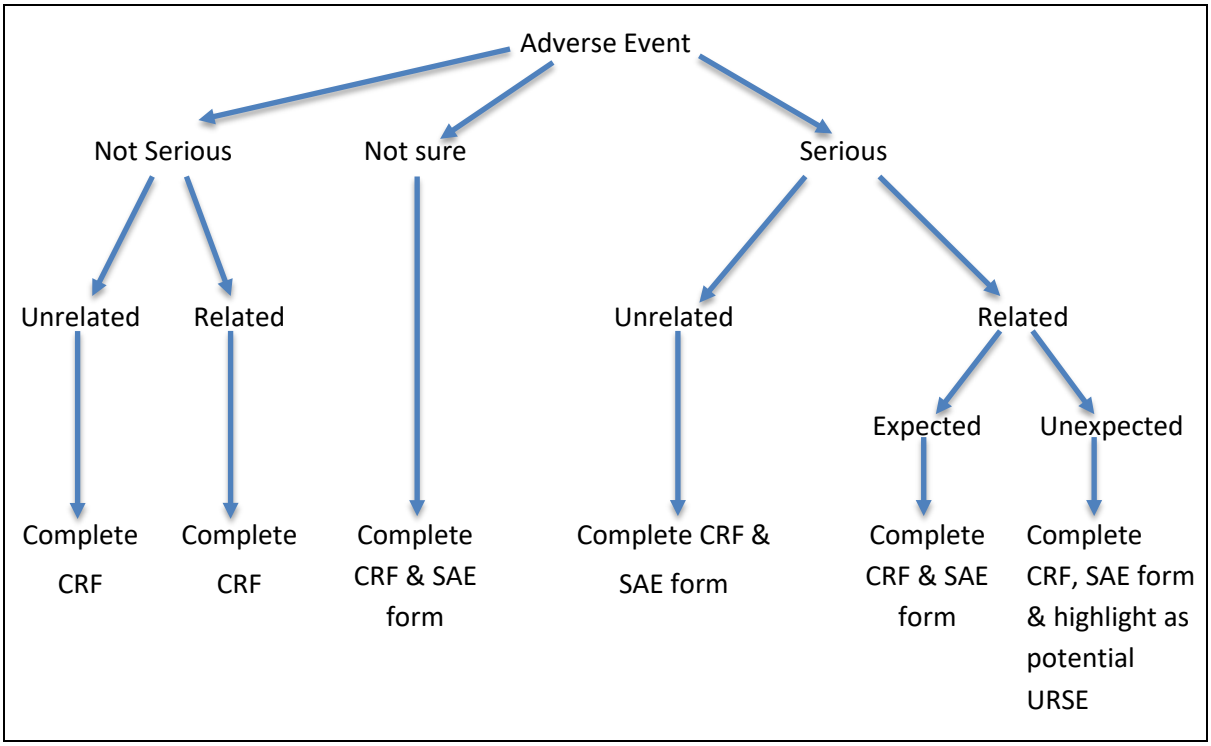
16. APPENDICES

16.1. Appendix 1 - Safety Reporting Diagram



Contact details for reporting SAEs

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

16.2. Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

{Enter all amendments to the protocol here whether substantial or non-substantial. Substantial amendments will require approval by the NHS REC. Non-substantial amendments should be sent to the NHS REC for acknowledgement only}