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Bristol Randomised Trials Collaboration

University of BRISTOL

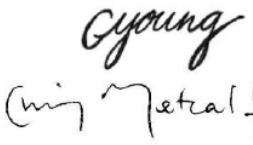
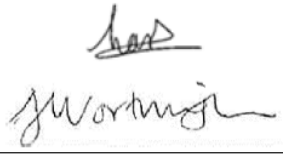
Bristol Randomised Trials Collaboration (BRTC)

UNBLOCS

Uri**N**ary o**B**struction relieved by **L**aser **O**r **C**onventional **S**urgery

Statistical Analysis Plan

Version 1.0 (22.11.17)

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
Name	**Role**	**Signature**	**Date**
Grace Young Chris Metcalfe	Authors		18/12/17 18/12/17
Jonathan Cook	DMC chair		7/12/17
Hashim Hashim Jo Worthington	Chief Investigator Trial Manager		20/12/17 20/12/17

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Abbreviations

AE	Adverse event
BPO	Benign Prostatic Obstruction
BRTC	Bristol Randomised Trials Collaboration
CACE	Complier Average Causal Effect
DRE	Digital Rectal Examination
GA	General Anaesthetic
ICIQ-MLUTS	International Consultation of Incontinence Questionnaires on Male LUTS
ICIQ-MLUTS-sex	International Consultation of Incontinence Questionnaires on Male LUTS sexual function
IIEF	International Index of Erectile Function Questionnaire
IPSS	International Prostate Symptom Score
ITT	Intention To Treat
LUTS	Lower Urinary Tract Symptoms
MAR	Missing At Random
NHS	National Health Service
PI	Principal Investigator
PIS	Patient Information Sheet
Qmax	Maximum urinary flow rate
QoL	Quality of Life
ThuVARP	Thulium laser transurethral vaporesection of the prostate
TURP	Transurethral Resection of the Prostate
UK	United Kingdom
UTI	Urinary Tract Infection

1. Introduction & Purpose

This document details the proposed rules and presentation to be followed, as closely as possible, when analysing and reporting the main results from the **UNBLOCS** trial: Urinary obstruction relieved by laser or conventional transurethral surgery

The purpose of the plan is to:

- Pre-specify the analysis prior to examining the outcome data
- Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of *a priori* and *post hoc* analyses respectively is appropriate.
- Explain in detail how the data will be handled and analysed to enable others to perform the analysis in the event of sickness or other absence.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available, if required, to journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the analysis plan, but, if reported, the source of such a *post-hoc* analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. Trial Synopsis

This is a summary of the study design as described in the study Protocol (version 10, 4th May 2017) with the single purpose of ensuring an informed statistical analysis. For all other purposes reference MUST be made to the current version of the protocol (if different from version noted above).

2.1 Rationale

As men get older their prostates get bigger. This commonly results either in urinary retention, when the man cannot pass urine, or in bothersome lower urinary tract symptoms (LUTS) secondary to benign prostatic obstruction (BPO). If medical therapy fails to improve these symptoms, men often request surgery to reduce their LUTS, and relieve the obstruction, in order to allow them to void better, and prevent the complications associated with BPO.

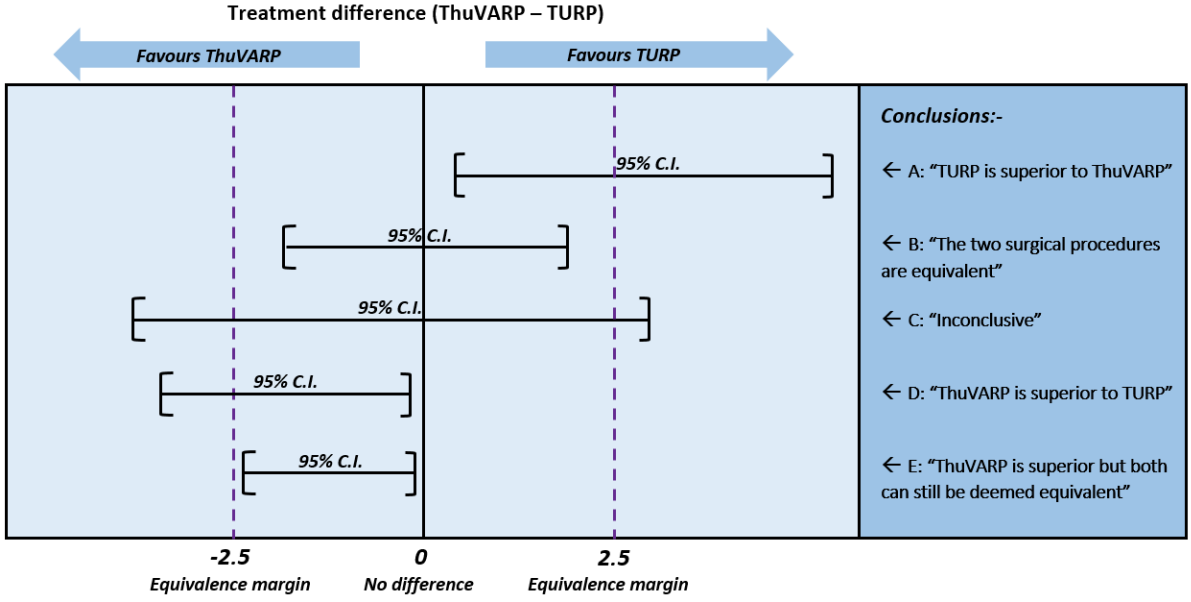
Around 25,000 prostate operations are performed annually in the UK for men with benign prostatic obstruction (BPO) to relieve obstruction, with transurethral resection of the prostate (TURP), the gold standard operation, accounting for around 80% of these operations. TURP has been used widely

for the last 40 years, and although it is generally a successful procedure, it is associated with small but significant risks for the patient.

Currently available data suggests that thulium laser transurethral vaporesection of the prostate (ThuVARP) can potentially reduce blood loss, shorten hospital stay with an increased proportion conducted as day-cases, allow an earlier return to normal activities, shorten duration of catheterisation and reduce incidence of TUR syndrome. Thus the ThuVARP procedure has the potential to offer significant health and quality of life benefits to patients at reduced cost to the NHS. The key aim of this research is to determine whether ThuVARP is equivalent to TURP in men with lower urinary tract symptoms secondary to benign prostatic obstruction (BPO) treated within the NHS, judged on a patient reported symptom severity score (IPSS) and the maximum urine flow rate (Qmax); therefore two primary outcomes.

2.2 Trial Design

UNBLOCS is a two arm, multi-centre, pragmatic, parallel-group RCT randomising men with benign prostatic obstruction (BPO) to either ThuVARP or TURP. Randomisation will be at the patient level so men will be randomised to receive either ThuVARP or TURP. The study was designed as an equivalence trial with an equivalence margin of 2.5 on the IPSS scale and 4ml/s on the Qmax scale. With respect to the IPSS outcome, if the 95% confidence interval of the difference (ThuVARP-TURP) lies above 2.5 or below -2.5 then the two surgical procedures will be deemed non-equivalent. Therefore our null hypothesis is that a difference of at least 2.5 exists.



[Adapted from Piaggio G, Elbourne DR et al.[i]]

In the scenarios illustrated above, scenarios **B** and **E** would result in the conclusion that the two procedures are equivalent. However, in scenarios **A** and **D** one may be considered superior to the other, given that testing first for equivalence before superiority does not require a statistical penalty

for multiple testing.[ii] The illustration is very similar for the Qmax outcome with the signs reversed (as higher values are positive outcomes) and an equivalence margin of 4 rather than 2.5.

2.3 Trial Centres

Men suitable for prostate surgery will be recruited and operated on at seven centres; four university teaching hospitals (Bristol, Aberdeen, Newcastle, Leeds) and three district general hospitals (Swindon, Cheltenham, Truro). As this is a pragmatic study, centres will continue to use their usual practices, e.g. monopolar or bipolar TURP.

2.4 Study Population

2.4.1 Target Population

Men over the age of 18 who are suitable for prostate surgery. Men may request surgery to reduce their LUTS, relieve obstruction and prevent complications associated with BPO, e.g. UTI.

2.4.2 Inclusion Criteria

- As this is a pragmatic trial, it will include men (aged≥18) who are suitable for TURP referred to secondary care for assessment with a view to requiring benign prostatic obstruction (BPO) surgery for either bothersome lower urinary tract symptoms (LUTS), or urinary retention, secondary to BPO.

2.4.3 Exclusion Criteria

- Neurogenic LUTS (these patients do not usually require BPO surgery).
- Prostate cancer.
- Previous prostate (methodological) or urethral surgery (methodological).
- Men with a PSA outside of the normal age-related range and who have not had prostate cancer excluded.
- Men who are unable to give informed consent or complete trial documentation. This assessment will be made by a study doctor or research nurse who has appropriate training and responsibility for taking consent.

2.5 Intervention

ThuVARP uses laser technology to vaporise and resect the prostate while TURP uses electric current to resect the prostate. ThuVARP essentially uses the same surgical skill-set as for the TURP procedure which is part of core practice for all urologists, including our trial surgeons who will perform both procedures. Transurethral resection of the prostate (TURP) is the ‘gold standard’ operation to relieve obstruction in the UK and worldwide, and has been the most frequently performed procedure for 40 years.

2.6 Compliance

As this is a pragmatic trial, surgical procedure and postoperative care will be according to local centre practice. Concomitant procedures will be recorded and reported.

To promote fairness in the assessment of the outcomes of the operations, participants will not be informed of their study arm allocation, although their GP will be able to access this information, and participants will be made aware of this, and the reason behind it, before consent. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

2.7 Research Objectives

2.7.1 Primary

(1) What is the relative clinical effectiveness of ThuVARP and TURP in improving patient reported lower urinary tract symptoms (LUTS) as measured by the International Prostate Symptoms Score (IPSS) patient reported questionnaire, and the objective measure of maximum urinary flow rate (Qmax), 12 months after surgery? *Where a 2.5 point difference on the IPSS scale and 4ml/s difference on the Qmax is considered equivalent.*

2.7.2 Secondary

(1) How do the two procedures compare in terms of peri-operative outcomes?
   - *Clavien Dindo scoring of surgical complications*
   - *Length of hospital stay and transfusion rates*

(2) What is the cost-effectiveness of ThuVARP as compared to TURP in terms of the two primary outcomes and quality-adjusted-life-years (QALYs)?*

(3) What is the comparative impact of each treatment on patient-reported LUTS, erectile function, quality of life and general health at 6 weeks after randomisation/surgery, 3 months and 12 months
   - *ICIQ-MLUTS*
   - *ICIQ-MLUTSsex/IIEF-5*
   - *ICIQ-LUTSqol*

(4) What is the comparative satisfaction of men with each type of surgery?
   - *ICIQ-satisfaction*

(5) What is the comparative effectiveness of these operations in men who present with LUTS as opposed to urinary retention?

(6) What are men's experiences of both procedures, including those presenting with LUTS or urinary retention?*

*These objectives are not part of the statistical analysis

2.8 Recruitment

The UNBLOCS trial began recruitment in June 2014, with the first participant enrolled on 23 July 2014. Recruitment completed on 31st December 2016.

2.9 Randomisation Procedures

Randomisation will be at the patient level and will be stratified by centre and whether the patient was eligible due to bothersome LUTS or urinary retention. Randomisation will employ random sized blocking and will be carried out by the UKCRC accredited Bristol Randomised Trials Collaboration (BRTC).

2.10 Sample Size Calculation

2.10.1 Equivalence margin

The sample size calculation is based on the consideration that men randomised to ThuVARP should have clinical outcomes which are equivalent to those who are randomised to TURP. For the primary outcomes, a difference in LUTS score of no more than 2.5 points (on IPSS scale) and of 4m/s for Qmax suggests equivalence. The team felt that these were appropriate for the following reasons:

- The minimally clinically important difference (MCID) for the IPSS score is generally accepted to be a 3 point difference, however a previous trial[iii] of ThuVARP vs. TURP used an MCID of 2 points. This previous trial witnessed a very small difference of only 0.4 on the IPSS scale. The team felt that a level between these would be more suitable.
- There is no minimally clinical important difference in flow rate that is accepted in the literature, however 2ml/s has been quoted previously[iv].
- Discussions between clinicians, both in the trial team and with other urologists, were used to reach an overall consensus that the maximum acceptable differences would be a flow rate of 4ml/s and 2.5 points or less on the IPSS.

2.10.2 Sample size

This study is powered to establish equivalence in clinical improvement. A Chinese trial[iii] observed differences of 0.4 ml/s (95% CI: -2.0 to 2.8) in Qmax and 0.4 units (-0.7 to 1.5) in IPSS between ThuVARP and TURP. Variability (standard deviation; SD) in data at 12 months was approximately 6.0 ml/s (Qmax) and 3.0 units (IPSS), but previous trials of TURP report greater variability, around 9 ml/s (Qmax) and 5 units IPSS[v,vi]. We have specified differences of 4 ml/s in Qmax and 2.5 units in IPSS, as demonstrating equivalence. Equivalence studies often use an alternative hypothesis of a difference of zero between treatments. However, the Chinese trial observed differences of around 0.4 ml/s and 0.4 units for Qmax and IPSS. Incorporating these as alternative hypotheses ensures adequate power to demonstrate equivalence if treatments are indeed similar but not identical.

Assuming SDs of 9 ml/s for Qmax and 5 units for IPSS, the target sample size for patients needed to complete the 12-month follow-up was 163 patients in each group. Using NQuery Advisor, this will provide 85% power to demonstrate equivalence for Qmax and just over 90% power for IPSS, at a two-sided alpha of 5%. Assuming 20% loss to follow-up following randomisation, it was necessary to recruit 410 men in total. This loss to follow-up is a conservative estimate from our experience of previous trials. However, we are aiming to reduce loss to follow-up through letter, text and telephone reminders to patients.

2.11 Blinding

To reduce bias in the assessment of outcomes, participants were not informed of their study arm allocation, although their general practitioner (GP) can access this information. Participants were informed that, although it would be preferred that they did not know which operation they have had; their GP will not be prevented from giving them this information if they request it. We anticipated that some men will ask for, or discover, their allocation at some point during the study and we will be asking them to reveal when and how they became aware of this in the 12-month follow-up questionnaire.

All investigators remained blinded throughout recruitment and analysis of patients. The senior statistician, Chris Metcalfe had not seen any data when writing this SAP and will remain blinded throughout the analysis. The junior statistician, Grace Young, had access to a small subset of patients (20) while helping to write the analysis plan.

3. Statistical Analysis

3.1 Software

Stata 14.1 (or a later version) will be used for analysis of the UNBLOCS study.

3.2 Data Collection

Data will be collected at certain points for the various data collection forms. The IPSS score will have been collected at baseline, 6 weeks, 3 months and 12 months whereas the Qmax will be collected at baseline, 3 months and 12 months. The ICIQ urinary, sexual, QoL and satisfaction questions will also be asked at these time points; as will the EQ5D.

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			
Time point	Baseline	Day of surgery	Post-operative	6 weeks	3 months	12 months
Case report form	✓	✓	✓		✓	✓
ICIQ-Bladder diary	✓				✓	✓
Maximum urinary flow rate (Qmax)	✓				✓	✓
Post-void residual and Voided volume	✓		✓		✓	✓
Full blood count	✓		✓			
Urea & Electrolytes	✓		✓			
IPSS	✓			✓	✓	✓
ICIQ-MLUTS	✓			✓	✓	✓
ICIQ-MLUTSsex/IIEF-5	✓			✓	✓	✓
ICIQ-LUTSqol	✓			✓	✓	✓
EQ-5D-5L	✓			✓	✓	✓
ICIQ-satisfaction				✓	✓	✓

3.3 Distributions

Where the distribution of the outcomes is approximately normal, mean values with standard deviations will be presented. For baseline characteristics, where the distribution of the outcome is not approximately normal, suitable transformations or medians and interquartile ranges (IQR) will be presented. For binary/categorical variables, a number and percentage will be presented.

For the continuously measured outcomes in the primary and secondary analyses, where outcomes are clearly non-normal, transforming to improve the normality of the residuals in the regression models will be explored. The choice of whether or not to transform variables, and if so which transformation to use, will be decided by considering:

(1) The distribution of the variable

(2) The distribution of residuals from regression models
(3) The ease of interpreting results following any given transformation compared with no transformation
(4) Whether main results/conclusions are influenced by the transformation or not.

3.4 Withdrawal

Participants will remain in the trial unless they choose to withdraw or if they are unable to continue for a clinical reason. If a participant withdraws consent, further participant questionnaires will not be collected. However permission will be sought for the research team to continue to collect outcome data from their health care records. Participants are informed in the PIS that they have the right to withdraw all personal data held by the study. Study specific procedures for a participant's change of permissions, or withdrawal, are outlined in the relevant trial working guidelines that are provided to each site. This guidance includes mandatory reporting procedures by sites to the central office (BRTC). The withdrawals from both arms will be recorded and a chi squared test will be performed to compare the difference in the number of withdrawals between the arms. Men may also choose to change permissions, e.g. request no further clinical tests but continue completing questionnaires, these will be compared in the same way.

3.5 Baseline Characteristics

Baseline characteristics will be compared between the two arms by reporting relevant summary statistics in order to determine whether any potentially influential imbalance occurred, by chance, between the two arms. Characteristics will be reported as means (sd), medians (IQR) or number (%) depending on the nature of the data and its respective distribution as defined in section 3.3.3. If the baseline characteristics of the two groups differ by more than 10% or half a standard deviation then the effect of this variable on the outcome will be investigated in a sensitivity analysis.

3.6 Analysis of Effectiveness

3.6.1 Analysis Populations

•**ITT Analysis set:** All randomised participants: analyses will be based on the intention-to-treat principle (ITT), analysing men in the groups to which they were randomised.

•**Per protocol analysis set:** Only including those who complied with their allocated treatment and did not deviate from the protocol.

3.6.2 Primary Analysis

The primary comparative analyses will be conducted on an 'as allocated' basis and will employ **multivariable linear regression** to investigate equivalence in Qmax and IPSS between ThuVARP and TURP at 12 months. The null hypothesis is that the two surgical procedures differ by at least 2.5 and

4 in their IPSS and Qmax score respectively, while the alternative hypothesis is that the two procedures are equivalent. Analyses will adjust for stratification variables (centre and baseline LUTS/retention). Interpretation of results will focus on observed differences, and 95% confidence intervals for the between-group comparisons, to determine whether clinically important differences between ThuVARP and TURP are unlikely. The null hypothesis for the primary analysis is "difference in IPSS/Qmax between the groups".

$$y_i = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + e_i$$

Where y is IPSS/Qmax, β_1 is the parameter regression co-efficient for group and x_1 is the variable group (1= ThuVARP, 0=TURP). Variables x_2 and x_3 are the potential confounding variables that are being adjusted for; centre and retention status. e_i represents the error term for patient i.

As stated in the protocol, the primary analysis will account for missing data. We will explore the implications of this by conducting a complete case analysis as a sensitivity analysis. Missing data for the primary outcome, assumed to be MAR (missing at random), will be imputed under conservative assumptions and the effect of missing data investigated. The handling of missing data will follow the principles specified in the EMA/CPMP/EWP/1776/99 Rev1 and any changes to the methods described here will be fully justified in the study report and publication. For the imputation model adopted, a pre-specified random seed of 525 has been chosen. The trial team anticipates that missing data will be MAR and therefore a multiple imputation approach is appropriate to evaluate the difference in treatments, at 12 months, while accounting for missing IPSS/Qmax levels. Data from the 6 week and 3 month time points will be used to inform the imputation process. The main primary analysis will not adjust for baseline IPSS/Qmax score as those with retention are unlikely to have relevant or appropriate scores. We will however factor baseline IPSS and baseline Qmax in subsequent sensitivity analyses.

3.6.3 Secondary Analyses

(1) Clavien-Dindo (scale 1-5) classification of surgical complications; the number of complications experienced per patient will be explored, along with the worst event per patient using **ordinal logistic regression**. If there are sufficient numbers then we will also explore the data at the event level, using descriptive data only.
    1. Deviation from normal postoperative course without the need for further interventions (pharmaceutical, surgical etc.)
    2. Requiring pharmacological treatment
    3. Requiring surgical intervention (a) not under GA or (b) under GA
    4. Life-threatening complication: (a) single or (b) multi organ failure
    5. Death of patient

(2) Length of hospital stay will be analysed using **linear regression** while transfusion rates will be measured using **logistic regression**.

(3) Comparative impact of each treatment on patient-reported LUTS, erectile function, quality of life and general health at 6 weeks after randomisation/surgery, 3 months and 12 months. Measured using the:
    - ICIQ Male LUTS (ICIQ-MLUTS)

- ICIQ sexual function in Male LUTS (ICIQ-MLUTS-sex)
- IIEF-5
- ICIQ quality of life (ICIQ-LUTSqol)
- IPSS QoL

These measures will be analysed using **linear and logistic regression** as appropriate.

(4) Comparative satisfaction of men with each type of surgery, measured using the ICIQ-satisfaction, analysed using **logistic and ordinal logistic regression** as appropriate.
(5) Post-operative catheterisation time, a continuous variable, measured from the time of surgery to the time of TWOC. This will be measured using a time to event analysis technique such as a **cox proportional hazards model**. We will also report on whether the patient still has a catheter at 3 month and 12 months, analysed using **logistic regression**]
(6) Haemoglobin – blood loss during surgery, analysed using **linear regression**.
(7) Serum sodium – absorption of irrigation fluid, analysed using **linear regression**.
(8) Post-void residual urine, analysed using **linear regression**.

Should the assumptions of these analyses not be met, alternative transformations or non-parametric methods may be utilised.

3.6.4 Subgroup analyses

Formal tests of interaction between the dichotomised variables and treatment pathway will be carried out to test whether treatment effect differs between patients. These subgroup analyses will be applied to the two primary analyses (IPSS and Qmax score):

- Baseline diagnosis of LUTS vs. urinary retention
- Age (split by the median age)
- Pre-operative prostate size measure by DRE (small <40g, medium 40-60g, large 60-80g and very large >80g)
- Patients with or without co-morbidities at baseline (based on the Charlson Index)

In the protocol we had specified that we would look at the length of stay of procedures (daycase or inpatients). However, it was later decided that this would be more suitable as an outcome only as the baseline intention would be unlikely to alter the treatment effect on IPSS scores/Qmax.

3.6.5 Sensitivity Analysis

Several sensitivity analyses will be conducted to test the robustness of the results from the statistical analyses, and in some cases, to increase understanding of the relationship between the dependent and independent variables:

1. Complete case analysis

The primary analysis will be repeated, without imputation for missing variables

2. Per Protocol analysis

The Per Protocol analysis allows assessment of treatment effect among those who received the treatment that they were assigned to. Both TURP and ThuVARP have an array of concomitant treatments; the appropriateness of which will be agreed in advance of analysis.

3. CACE analysis

The Complier Average Causal Effect (CACE) analysis allows unbiased assessment of treatment effect which analyses patients according to the treatment they received and uses random allocation as an instrumental variables.

4. Removal of patients

Patients who have found out their allocation (not including those who guess correctly) prior to completing the 12 month questionnaire and follow up will be removed from the cohort in this sensitivity analysis.

5. Adjustment for baseline

The two primary outcomes (IPSS and Qmax) will be adjusted for their respective baseline measures. Clinically sensible values will be imputed for those with retention, such as the lowest score of those recorded. If this proves difficult, baseline measures may be graded by severity and those with catheters placed in the most severe category.

6. Adjustment for imbalance at baseline

As described in section 3.5, covariates that differ at baseline by more than half a standard deviation (or 10%) will be added to the model concurrently to investigate their effect on the difference observed between the two groups.

7. Type of TURP/surgery

Although originally listed in the protocol as a sub group analysis we will analyse TURP separately alongside ThuVARP; therefore comparing 3 groups ThuVARP, monopolar TURP and bipolar TURP.

8. Surgeon effects

A mixed-effects model will be conducted that includes the surgeon as a random effect in the main primary models. If there are enough surgeons per centre, we will include centre as a fixed effect and surgeon as a random effect. If there are too few then we will simply replace centre with surgeon in the model.

3.6.6 Exploratory Analyses

Bladder diaries will be collected and analysed. Although not part of this analysis plan, these will be explored in future analyses.

4. Final report tables and figures (subject to change)

Figure 1. CONSORT diagram

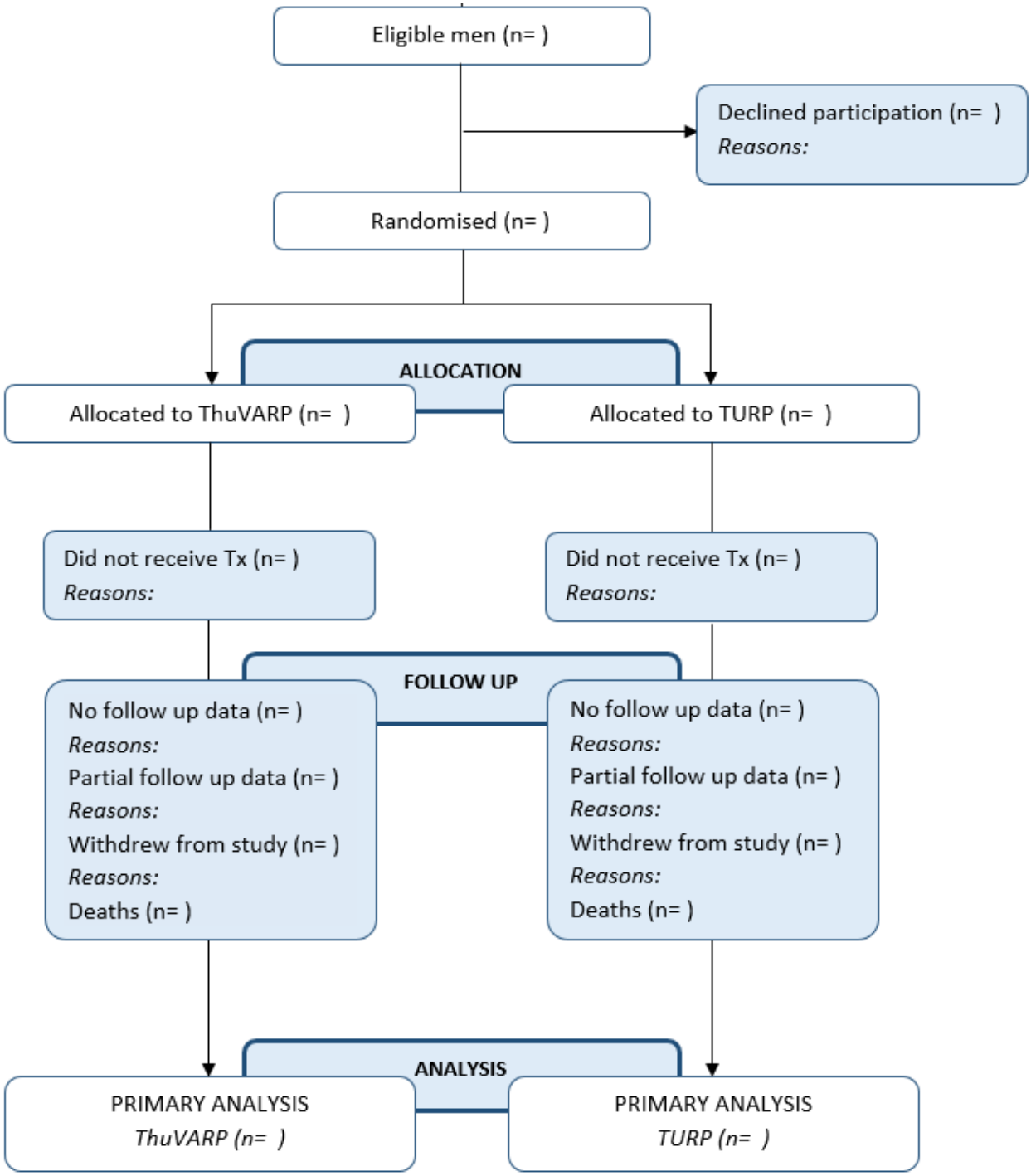


Table 1. Baseline Characteristics between each treatment arm

		ThuVARP		TURP
	n*	***Mean (SD)* or n (%)**	**n***	***Mean (SD)* or n (%)**
Total number of participants				
Age(years)				
Bothersome LUTS				
Urinary retention				
BMI (on day of surgery)				
Centre				
Bristol				
Aberdeen				
Newcastle				
Leeds				
Swindon				
Cheltenham				
Truro				
Ethnicity				
White				
Black/African/Caribbean/Black British				
Mixed/Multiple ethnic groups				
Asian/Asian British				
Other ethnic group				
Disclosure declined				
Comorbidities at baseline (from the Charlson Comorbidity Index)				
None				
One				
More than one				
Urinary measures				
Maximum flow rate (Qmax)				
Post-void residual (PVR)				
Voided volume (VV)				
Has the patient had Urodynamics?				
Catheterisation				
In use				
Intermittent				
Indwelling				
Prostate tests				
PSA test				
TRUS				
DRE				
Prostate size: Normal				
Prostate size: Suspicious				
Blood tests				
Is the patient on anticoagulants?				
Sodium (total)				
Creatinine				
Haemoglobin				
Platelets				
White cell count				

Haematocrit	
IPSS: Symptom severity at baseline	
Incomplete Emptying	
Frequency	
Intermittency	
Urgency	
Weak Stream	
Straining	
Nocturia	
Total IPSS score	
IPSS QoL	
ICIQ MLUTS	
Voiding score~	
Incontinence score#	
Daytime frequency (>8 times)	
Nocturia (>1 times per night)	
ICIQ MLUTS – sexual matters	
Erections (reduced or none)	
Ejaculation (reduced or none)	
Painful ejaculation (Yes)	
Urinary symptoms affected sex life?	
IIEF - 5	
Erectile dysfunction score+	

*n analysable, ~On a scale of 0-20 with larger scores indicating more severe symptoms, #On a scale of 0-24 with larger scores indicating more severe symptoms, +Lower scores indicate more severe erectile dysfunction (5-7=severe, 8-11=moderate, 12-16=mild to moderate, 17-21=mild, 22-25=none)

Table 2. Primary and secondary outcomes for PROMS and Qmax, difference between arms

Variable	ThuVARP *Mean (SD)*	TURP *Mean (SD)*	Difference in means* (95% C.I.)	P value*
Primary analysis				
TOTAL IPSS Score				
Qmax score				
Secondary analysis (ICIQ-MLUTS)				
ICSmaleVS (voiding scale)~				
ICSmaleIS (incontinence scale)#				
Daytime frequency (>8 times)				
Nocturia (>1 times per night)				
Secondary analysis (ICIQ-MLUTSsex)				
Erections (reduced or none)				
Ejaculation (reduced or none)				
Painful ejaculation (Yes)				
Urinary symptoms affected sex life?				
Secondary analysis (IIEF)				
Erectile dysfunction score+				

*Adjusted for centre and whether the patient had retention or LUTS at baseline

~Voiding scale, on a scale of 0-20 with larger scores indicating more severe symptoms

#Incontinence scale, on a scale of 0-24 with larger scores indicating more severe symptoms

+Lower scores indicate more severe erectile dysfunction (5-7=severe, 8-11=moderate, 12-16=mild to moderate, 17-21=mild, 22-25=none)

Table 3a. Surgical complications and Clavien Dindo scores per patient~

Variable	ThuVARP	TURP	Difference*	P value
	n (%)	n (%)		
Bleeding				
Not experienced				
CD grade I				
CD grade II				
CD grade III				
CD grade IV				
CD grade V				
Infection (sepsis, UTI, abscess)				
Not experienced				
CD grade I				
CD grade II				
CD grade III				
CD grade IV				
CD grade V				
Retrograde ejaculation				
Not experienced				
CD grade I				
CD grade II				
CD grade III				
CD grade IV				
CD grade V				
.....				
Not experienced				
CD grade I				
CD grade II				
CD grade III				
CD grade IV				
CD grade V				

*Ordinal logistic regression adjusted for centre and whether the patient had retention or LUTS at baseline, ~Where patients experienced multiple grading within one complication type, the highest was taken

Table 3b. Additional surgical outcomes

Variable	ThuVARP n (%)/*Mean(SD)*	TURP n (%)/*Mean(SD)*	Difference* (95% C.I.)	P value*
Surgery outcomes				
Length of hospital stay (hours)				
Transfusion required (Y/N)				
Post-operative catheterisation time				
Catheter required at 3m?				
Catheter required at 12m?				
Haemoglobin – blood loss				
Serum sodium				
Post-void residual volume				

Table 4. Secondary Outcome. Satisfaction with treatment

Variable	ThuVARP n(%)	TURP n(%)	Difference* (95% C.I.)	P value*
Overall scores				
Overall how satisfied were you[1] (0-10)?				
Median total questionnaire score[2] (iqr)				

*Adjusted for centre and whether the patient had retention or LUTS at baseline
[1]Higher scores indicate better satisfaction
[2]Lower scores indicate better satisfaction

Table 5. Secondary Outcome. Quality of life

Variable	ThuVARP n(%)/*Mean(SD)*	TURP n(%)/*Mean(SD)*	Difference* (95% C.I.)	P value*
IPSS QoL				
Quality of life (0-7)				
ICIQ QoL subscores~				
Role limitations				
Physical limitations				
Social limitations				
Personal relationships				
Emotions				
Sleep/energy				
Severity measures				
ICIQ Urinary symptoms effect on...				
Getting embarrassed				
Overall interference with everyday life				

* Adjusted for centre and whether the patient had retention or LUTS at baseline, ~Based on the Kings Health Questionnaire

Table 6. Sensitivity Analyses: IPSS and Qmax Scores, difference between arms

Variable	ThuVARP *Mean (SD)*	TURP *Mean (SD)*	Difference in means* (95% C.I.)	P value*
Sensitivity: IPSS Symptom Score				
Complete case analysis				
Per protocol[1]				
CACE analysis[2]				
Removal of patients[3]				
Adj. for baseline[4]				
Adj. for imbalance[5]				
Type of TURP/surgery[6]				
Surgeon effects[7]				
Sensitivity: Qmax Score				
Complete case analysis				
Per protocol[1]				
CACE analysis[2]				
Removal of patients[3]				
Adj. for baseline[4]				
Adj. for imbalance[5]				
Type of TURP/surgery[6]				
Surgeon effects[7]				

*****Adjusted for centre & whether the patient had retention or LUTS at baseline, [1]Removing those who did not comply with their randomised treatment, [2]Unbiased estimates to account for patient crossover, [3]Patients who found out their allocation prior to completing the 12 months questionnaire, [4]Respective baseline measures for the IPSS and Qmax, [5]Imbalances at baseline by more than 10%/0.5 SDs, [6]Comparison of 3 groups: ThuVARP, monopolar TURP and bipolar TURP, [7]A mixed effects model will be conducted that includes the surgeon as a random effect

Table 7. Subgroup Analyses: Primary outcomes

Variable	IPSS score at 12 months[£]		Qmax at 12 months[£]	
	Subgroup specific MD (95% C.I)	Interaction effect MD (95% C.I); p	Subgroup specific MD (95% C.I)	Interaction effect MD (95% C.I); p
Subgroup analyses				
Baseline diagnosis				
LUTS				
Urinary retention				
Age				
<Median				
≥Median				
Peri-operative prostate size (DRE)				
Small (<40g)				
Medium (40-60g)				
Large (60-80g)				
Very large (>80g)				
Comorbidities at baseline				
With				
Without				

MD refers to difference in means, [£]Linear regression model adjusting for centre and baseline diagnosis where appropriate

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