University of BRISTOL

North Bristol NHS Trust

UriNary oBstruction relieved by Laser Or Conventional Surgery

A randomised controlled trial to determine the clinical and cost effectiveness of thulium laser transurethral vaporesection of the prostate (ThuVARP) versus transurethral resection of the prostate (TURP) in the National Health Service (NHS).

PROTOCOL

Version 9

01/10/2016

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Study Management Group

Sponsor

North Bristol NHS Trust Research & Innovation (NBTR&I)
Trust Headquarters, Beckspool Road, Frenchay, Bristol BS16 1JE

Chief Investigator

Mr Hashim Hashim
Consultant Urological Surgeon
Clinical Research Centre
Beaufort Way
Southmead Hospital
Bristol BS10 5NB
Tel: +44 117 414 8107
Fax: +44 117 414 8149
email: h.hashim@gmail.com

Co-investigators

Professor Paul Abrams, Professor of Urology, North Bristol NHS Trust
Mr Tobias Page, Consultant Urological Surgeon, Newcastle Upon Tyne Hospitals NHS Foundation Trust
Dr Nikki Cotterill, Specialist Health Outcomes Researcher, North Bristol NHS Trust
Dr Sian Noble, Senior Lecturer in Health Economics, University of Bristol,
Dr Sara Brookes, Senior Lecturer in Health Services Research, University of Bristol
Dr Athene Lane, Associate Director of BRTC, University of Bristol
Mr K. Satchi Swami, Consultant Urological Surgeon, NHS Grampian

Statistician

Sara Brookes

Study management

Bristol Randomised Trials Collaboration (BRTC)
University of Bristol
School of Social and Community Medicine

Study contact

General queries, study documentation, data collection to Dr Athene Lane
Clinical queries to Mr Hashim Hashim

This protocol describes the UNBLOCS study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Table of Contents

Glossary of abbreviations

AE	Adverse Event
BAUS	British Association of Urological Surgeons
BPO	Benign Prostatic Obstruction
BRTC	Bristol Randomised Trials Collaboration
CI	Chief Investigator
CG	Clinical Guideline
CLasP	A prospective randomised trial comparing transurethral resection of the prostate and laser therapy in men with chronic urinary retention
CRF	Case Report Forms
DMC	Data Monitoring Committee
EAU	European Association of Urology
EQ-5D-5L	EuroQol Group's 5 dimension health status questionnaire
FBC	Full Blood Count
GCP	Good Clinical Practice
g/L	Grams per Litre
GP	General Practitioner
HES	Hospital Episodes Statistics
HoLEP	Holmium Laser Enucleation of Prostate
HTA	Health Technology Assessment
ICIQ-LUTSqol	International Consultation on Incontinence Questionnaire – Lower Urinary Tract Symptoms Quality of Life
ICIQ-MLUTS	International Consultation on Incontinence Questionnaire – Male Lower Urinary Tract Symptoms
ICIQ-MLUTSsex	International Consultation on Incontinence Questionnaire – Sexual Matters associated with Male Lower Urinary Tract Symptoms
ICIQ-satisfaction	International Consultation on Incontinence Questionnaire – Satisfaction
IIEF	International Index of Erectile Function
IMP	Investigational Medicinal Product
IPSS	International Prostate Symptom Score
ISCP	Intercollegiate Surgical Curriculum Programme
ISRCTN	International Standard Randomised Controlled Trial Number
LUTD	Lower Urinary Tract Dysfunction
LUTS	Lower Urinary Tract Symptoms
NCRI	National Cancer Research Institute

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
PI	Principal Investigator
PMG	Project Management Group
PP	Patient Panel
PROs	Patient Reported Outcomes
PVR	Post-Void Residual
QALY	Quality Adjusted Life Years
Qmax	Maximum Urinary Flow Rate
RCT	Randomised Controlled Trial
R&D	Research and Development
RUL	Resource Use Log
SD	Standard Deviation
SAE	Serious Adverse Event
SSA	Site Specific Assessment
ThuVARP	Thulium Vaporesection of the Prostate
TSC	Trial Steering Committee
TURP	Transurethral Resection of Prostate
U&Es	Urea & Electrolytes
UK	United Kingdom
UNBLOCS	UriNary oBstruction relieved by Laser Or Conventional Surgery
VV	Voided Volume
WBA	Work-Based Assessment

Keywords

Thulium, Laser, TURP, Prostate, Benign, Obstruction, Urinary Retention, Surgery

Study summary

Title

A randomised controlled trial to determine the clinical and cost effectiveness of thulium laser transurethral vaporesection of the prostate (ThuVARP) versus transurethral resection of the prostate (TURP) in the National Health Service (NHS).
Acronym: UriNary oBstruction relieved by Laser Or Conventional Surgery - the UNBLOCS trial.
Short title: Urinary obstruction relieved by laser or conventional transurethral surgery

Design

Randomised controlled parallel-group trial

Aims

The key aim of this research is to determine whether thulium laser transurethral vaporesection of the prostate (ThuVARP) is equivalent to transurethral resection of the prostate (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).

Primary outcome measures

Clinical effectiveness of ThuVARP and TURP in improving patient reported lower urinary tract symptoms (LUTS) as measured by the IPSS patient reported outcome questionnaire and the objective measure of Qmax, 12 months after surgery.

Secondary outcome measures

Peri-operative outcomes:

1. Clavien-Dindo classification of surgical complications [1]
2. Length of hospital stay and transfusion rates.

Patient reported outcomes

All patient reported outcomes (PROs) will be recorded at baseline, 6 weeks, 3 months and 12 months.

1. Cost-effectiveness of ThuVARP as compared to TURP in terms of the two primary outcomes and quality-adjusted-life-years (QALYs) measured using EQ-5D-5L (preference based general quality of life measure).
2. 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-MLUTS (for symptom bother), International Index of Erectile Function (IIEF), ICIQ-MLUTSsex (measures of erectile function), ICIQ-LUTSqol (condition specific quality of life score), and the EQ-5D-5L (preference based general quality of life measure) to assess the full impact of the intervention on patients and the NHS.
3. Comparative satisfaction of men with each type of surgery measured using ICIQ-Satisfaction (measures satisfaction with surgery outcomes).
4. Comparative effectiveness of these operations in men who present with LUTS as opposed to urinary retention measured using the ICIQ-MLUTS (for symptom bother), International Index of Erectile Function (IIEF), ICIQ-MLUTSsex (measures of erectile function) and ICIQ-LUTSqol (condition specific quality of life score).
5. Comparative resource use for the year following randomisation.
6. Men's experiences of both procedures, including both those presenting with LUTS or urinary retention via structured interview.

Population

Adult men over the age of 18

Eligibility

Inclusion criteria

Men suitable for TURP, either in urinary retention or with bothersome lower urinary tract symptoms (LUTS), secondary to BPO.

Exclusion criteria

Patients with:

- Neurogenic LUTS
- Prostate cancer
- Previous prostate or urethral surgery
- 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

Sponsor

North Bristol NHS Trust Research & Innovation (NBT, R&I)

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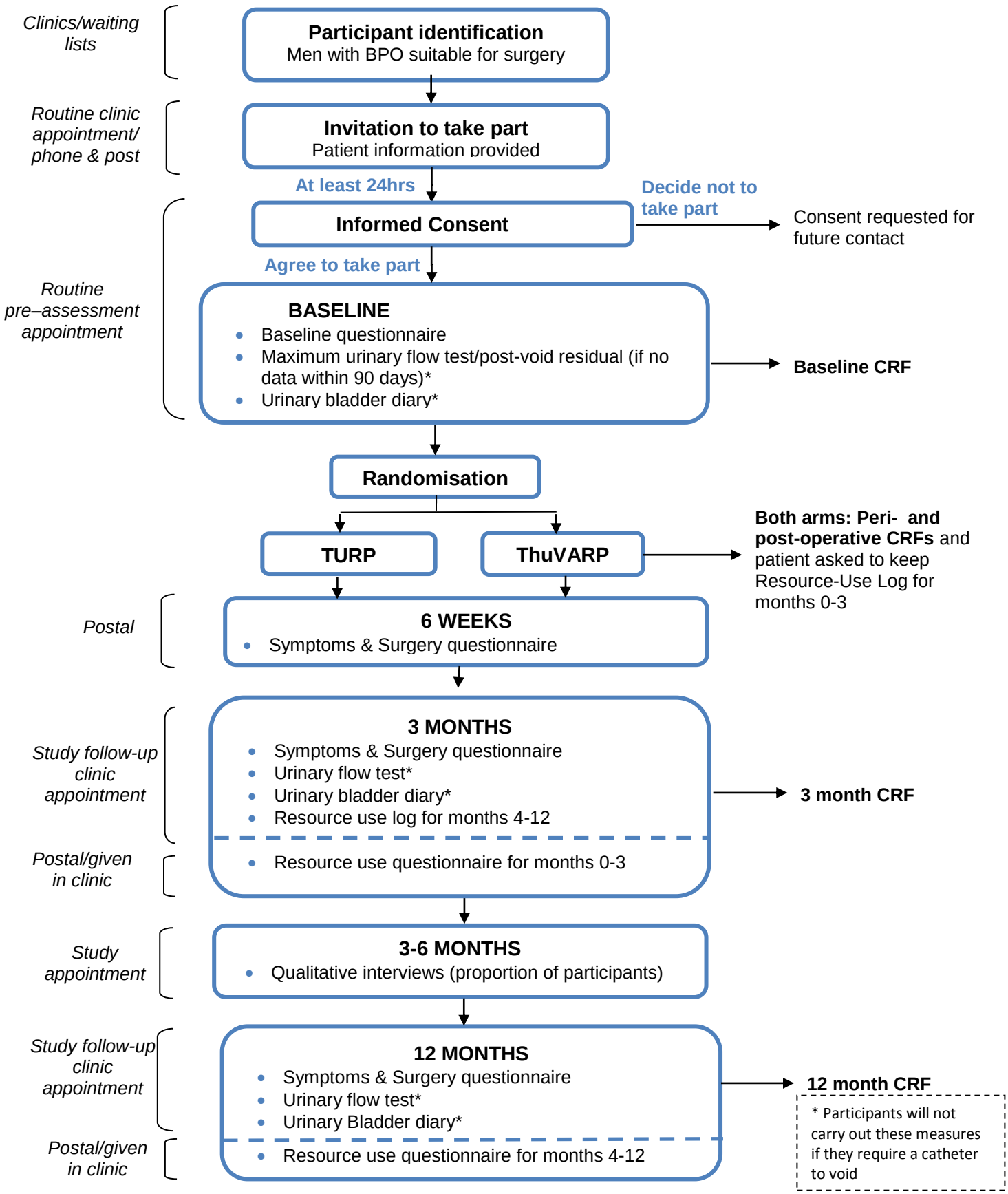
Study diagram



1. Introduction

1.1 Background

Around 25,000 prostate operations are performed annually in the UK for men with benign prostatic obstruction (BPO) to relieve obstruction, with TURP, the gold standard operation, accounting for around 80% of these operations. TURP has been used widely for the last 40 years and although various alternative approaches using lasers have been marketed, none have become widely used, for example, because of a long learning curve (e.g. HoLEP holmium laser), or inferior performance regarding clinical outcomes, reducing the wider uptake. In fact, recent HES data shows that the percentage of laser procedures has declined by about 2% from 2894 in 2009/10 to 2187 in 2011/12. This is despite the accepted advantages of laser prostatectomy, including reduced blood loss, less risk of hyponatraemia and reduced hospital stay.

For patients undergoing BPO surgery, recent NICE clinical guidelines CG97 [2] recommend offering TURP or holmium laser enucleation (HoLEP). Although HoLEP is a long established effective procedure, it is only used in a few centres, due to a very long learning curve. Personal communications with expert HoLEP surgeons in the UK and Europe indicate that HoLEP is not generalisable and certainly NICE recommends that this procedure is only performed in centres specialising in the technique.

1.1.1 Health Technology Assessment (HTA) Programme

Prostate surgery in the form of transurethral resection of the prostate (TURP) for benign disease has been largely unchanged for 40 years and men are still exposed to the similar morbidity and mortality they always were, despite small changes to TURP technology such as better equipment and diathermy machines. This trial is looking at a commonly performed surgical procedure (25,000 TURPs each year) within the HTA surgery themed call. The trial aim is to provide future value for money in the form of potential health gains, in terms of reduction in risks to men, and financial savings to the NHS.

1.1.2 Population

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. These can include renal failure, urinary tract infections, bladder stones, and the persistence of bothersome LUTS.

1.1.3 Intervention

We have chosen a thulium laser technique which vaporises and resects the prostate because it uses a surgical technique similar to TURP and, will therefore be quickly generalisable. Several, mainly laser, techniques have attempted to replace TURP over the years however none have become widely used. The recommendation from the 2010 NICE Clinical Guideline 97 [2] is to offer laser vaporisation or vaporesection techniques only as part of a randomised controlled trial that compares those techniques with TURP.

1.1.4 Comparator

Transurethral electro-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.

1.1.5 Outcome

Based on one randomised controlled trial and one non-randomised prospective controlled trial with small and medium-sized prostates, the European Association of Urology (EAU) guidelines have stated that thulium vaporesection of the prostate (ThuVARP) showed equivalent efficacy in comparison with TURP [3]. However the thulium patients had shorter catheterisation and hospitalisation times, with adverse events being lower than for TURP (intra-operative and post-operative bleeding; level of evidence 1b). Therefore, our study will

investigate these key outcomes in the UK setting and include the cost-effectiveness of ThuVARP over TURP, thus investigating value for money within the NHS setting.

1.1.6 The health problems addressed

Symptomatic benign prostatic obstruction (BPO) or urinary retention, severely affects a man's quality of life resulting in a worsening physical role, social functioning, vitality, and mental health [4]. Bothersome lower urinary tract symptoms (LUTS) secondary to BPO with an International Prostate Symptom Score (IPSS) of at least 11 and a maximum flow rate (Qmax) less than 15 ml/s, affects 2.5 million men aged 40-79 in the UK with 44,000 new cases diagnosed annually [5]. The number of patients with BPO is expected to grow by almost 50% by the year 2025, as it is a disease of older men [5]. Men usually present with LUTS, such as slow and intermittent urinary stream, or with urinary retention. LUTS may be treated by watchful waiting or drugs, but many will require prostate surgery, including almost all men who present in urinary retention (25,000 procedures are currently performed annually in the UK).

Transurethral resection of the prostate (TURP) has been the standard operation for LUTS and urinary retention for 40 years, and has not changed significantly, which is unusual in urology, where most other operations have been dramatically modernised using new technologies, such as laparoscopy and now robotics.

Although TURP is generally a successful procedure, it is associated with a small but significant risks; with a 30-day mortality of 0.3%; and a range of morbidities including TUR syndrome (1%) which is due to the absorption of irrigating fluid leading to confusion and collapse; haemorrhage during the operation (transfusion rate: 5%); and subsequent urinary tract infections (up to 20%) [6]. These morbidities result in delayed discharge and increased re-admissions, increased primary care resource utilisation, considerable distress to patients and additional costs to the NHS. As the operation is increasingly conducted on older men (42% of the TURP operations in 2011-2012 were on patients older than 75 years), these risks of surgery will continue to increase.

This study will evaluate a new laser technique called thulium laser transurethral vaporesection of the prostate (ThuVARP). The currently available data suggests that the advantages of ThuVARP are reduced blood loss, shorter hospital stay with an increased proportion conducted as day-cases, earlier return to normal activities, shorter duration of catheterisation, better visualisation during resection and reduced 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.

1.2 Rationale for current study

The well-known risks for both mortality and morbidity from TURP have meant that many alternatives have been assessed. However both the National Institute for Health and Care Excellence (NICE) and the European Association of Urology (EAU) have found the alternatives wanting, with the exception of holmium laser enucleation of the prostate (HoLEP) and ThuVARP (EAU only). The theoretical advantages of laser prostatectomy are accepted by the urological community, yet the numbers of laser prostatectomies are falling due either to the techniques' poor effectiveness or lack of generalisability. The current proper emphasis on patient safety using cost-effective procedures makes continued effort to find a cost-effective, generalisable alternative to TURP timely.

ThuVARP was first made available in 2004 in the UK but has only been compared in one randomised controlled trial (RCT) in China against TURP [7]. Consequently, the NICE guidelines have called for an RCT into 'the clinical and cost-effectiveness of laser vaporesection techniques compared with TURP in men with moderate to severe bothersome lower urinary tract symptoms (LUTS) considering surgery for bladder outlet obstruction, as the current evidence base is insufficient.

We have selected ThuVARP to compare directly against TURP to give results that are highly relevant to the NHS, because of its short learning curve and good immediate clinical outcomes. However to date, evidence of longer-term symptom improvement and quality of life gains is not available. We have waited to propose this trial until the development phase of ThuVARP was completed. As the procedure has not yet been widely taken

up across the UK, now is the ideal time to conduct the trial. Furthermore, discussions with the manufacturers and other urologists have not identified future developments with ThuVARP that would negate the potential results of this trial. Nonetheless, if a major modification, that would be expected to alter clinical outcomes, occurred in the near future this would be presented to the trial steering committee (TSC) and the trial data monitoring committee (DMC), to investigate whether the modified version should be incorporated by the trial.

We have already described the reasons why one of only two recommended laser techniques (HoLEP) has not, and will not, be generalisable. The situation with respect to the other recommended laser technique (ThuVARP in the EAU Guidelines) is that in the UK it is new and to date little used. Hence now is the optimum time to evaluate this most promising generalisable alternative to TURP.

An additional reason for early evaluation of ThuVARP is the promise it offers to convert BPO surgery from an in-patient operation into a day-case procedure. This is increasingly important both because of the increasing cost of in-patient beds, the emphasis on patients spending as little time in hospital as possible thereby avoiding morbidity and complications, such as hospital acquired infections, and the increasing pressure on in-patient beds from an ageing and increasingly co-morbid population.

This study will aim to benefit both men with BPO, and the NHS, by meeting a number of urgent needs.

1.2.1 Health need

ThuVARP would allow urologists to operate on a wider range of men, including potentially those who are more frail and older, but with less risk. It would also mean making the surgical treatment of BPO more efficient as procedures would be performed as day-cases, therefore reducing pressure on in-patient beds, which can be used for other purposes, and also improving the patient experience of the procedure by being a day-case. Having the operation as a day-case would also mean reducing the risk of it being cancelled due to bed shortages and therefore reducing the overall cost to the Trust and the NHS. This would allow service reconfiguration by converting most procedures to day-cases from the current 2 to 3 day stay in hospital for TURP.

1.2.2 Expressed need

NICE in its 2010 Male LUTS Guidelines [2] stated that the evidence base is inadequate to give clear guidance in terms of clinical and cost-effectiveness of laser vaporesection techniques. NICE identified that research in this area, in the form of a randomised controlled trial, would help inform future guidance on the use of laser vaporesection techniques for men with LUTS or urinary retention, who need surgery. The potential advantages of reduced blood loss, shorter hospital stay and earlier return to normal activities make laser vaporesection techniques attractive to both patients and healthcare providers, although there is uncertainty about the degree of symptom improvement and improvement in quality of life in the short and longer term, which this trial addresses.

1.2.3 Sustained interest and intent

The general population has an increased life-expectancy, men are living longer and so we have an ageing population. As men get older, their prostates enlarge and cause BPO which often requires surgery. Therefore, as the population ages, more operations will be needed on the benign prostate to relieve obstruction. There is therefore sustained interest in the condition and increasing need to find safer techniques than TURP.

Laser prostatectomy has been the subject of much urological interest for more than 20 years. We were involved in the only other government funded randomised controlled trial (RCT), the CLasP study, which compared TURP with side-fire laser, and with non-surgical treatment [8]. Unfortunately the laser technology at the time was relatively unsophisticated and the technique offered inadequate advantages for patients and NHS alike. Interest has remained high in the topic, however there has been a paucity of high quality research, and published case series have not shown good enough results. As there remains the need to find the safest and most cost-effective surgical treatment for BPO, the urological community will take note of high quality research

that provides data that confirms a new technique of value with advantages for patients and the NHS, over conventional surgery by TURP.

1.2.4 Capacity to generate new knowledge

Only a direct comparison RCT can generate the necessary evidence to allow the NHS to adopt or reject any laser technology for prostate operations. This study will help answer the NICE guidelines' research question and ensure that only new laser techniques of proven clinical and cost-effectiveness, are introduced to the market following the highest quality research, a randomised controlled trial. We have deliberately chosen to compare ThuVARP to the current gold standard (TURP) so that the knowledge will be directly applicable to the NHS. If the study is successful, ThuVARP can be introduced in an orderly manner. This methodology of performing a randomised controlled trial, that can confirm or refute cost-effectiveness, will prevent the long drawn out process of disinvestment that follows the haphazard introduction of "attractive" new techniques that subsequently fail to live up to their early promise: examples include balloon dilation and thermotherapy for BPO. Urological departments in Europe are full of redundant equipment used in techniques that were going to "revolutionise" the treatment of BPO, but were never properly evaluated.

1.2.5 Organisational focus consistent with the HTA mission

There have been no HTA-funded laser studies since the CLasP study, and no studies are known to be planned or in progress in the UK. There is an on-going commercial study in Germany that compares the efficacy and safety of ThuVARP with HoLEP, but is restricted to the minority of men who have prostates larger than 60 grams.

Also important, from the NHS point of view is that, for 100 procedures, the specific equipment and consumables cost of ThuVARP (~£27k) is cheaper than TURP (~£29k). However, the main benefit is a reduction of in-patient bed days (estimated at 35,000 per year), equating to an annual saving of £5.25 million. TURP has a median hospital stay of 2 days with only 0.5% of procedures done as day-cases, whilst most or all patients suitable for TURPs could be performed by ThuVARP with at least 50% as day-cases. These changes offer the possibility of reconfigurations of surgical services with a reduced dependency on in-patient provision and additional benefits for the patient experience.

1.2.6 Generalisable findings and prospects for change

Because ThuVARP uses a technique similar to that used in the existing standard operation of TURP, this laser procedure is potentially very quickly generalisable, as every urological trainee becomes competent in the technique of TURP by the time he or she becomes a consultant. This means that the "learning curve" will be short with an estimated maximum of 15 cases. Hence, if this trial were positive, as all urologists would wish to use a safer and equally effective procedure for BPO, the uptake of ThuVARP would be rapid.

1.2.7 Building on existing work

In summary, although there is little existing work on ThuVARP, promising initial evidence from one RCT shows that ThuVARP has equivalent clinical effectiveness when compared to TURP, albeit in a single Chinese centre. Our randomised study is designed to provide the high quality evidence, in an NHS setting with a range of patient reported, clinical and cost- effectiveness outcomes, which will underpin and inform future NICE guidance. We have also conducted the only government funded previous trial of laser versus TURP, the CLasP study [8].

2. Study objectives

The key aim of this research is to determine whether thulium laser transurethral vaporesection of the prostate (ThuVARP) is equivalent to transurethral resection of the prostate (TURP) in men with benign prostatic obstruction (BPO) treated within the NHS, judged on a patient reported symptom severity score (IPSS) and the maximum urine flow rate (Qmax).

We will answer the following primary question: 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 urine flow rate (Qmax), 12 months after surgery?

Secondary research questions are:

1. How do the two procedures compare in terms of peri-operative outcomes?
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?
4. What is the comparative satisfaction of men with each type of surgery?
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?

3. Study design

This is a multi-centre, pragmatic, randomised, controlled, parallel-group trial of thulium laser transurethral vaporesection of the prostate (ThuVARP) versus standard transurethral resection of the prostate (TURP) in men with benign prostatic obstruction (BPO). Randomisation will be at the patient level so men will be randomised to receive either ThuVARP or TURP. 410 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, for example, with respect to whether or not they do pressure-flow urodynamics as part of patient selection, or use monopolar or bipolar TURP.

Follow-up will be at 6 weeks, 3 and 12 months from randomisation (primary endpoints) for the patient reported outcome (PRO) International Prostate Symptom Score (IPSS), and at 3 and 12 months for the maximum urine flow rate (Qmax). Patients will be asked to complete other patient-reported outcomes at 6 weeks after surgery (by post), and after 3 and 12 months.

3.1 Study outcome measures

We have selected two key co-primary outcomes measured at 12 months based on a well-established and validated patient reported outcome (PRO), the International Prostate Symptom Score (IPSS), and the urodynamic clinical measure of maximum urine flow rate (Qmax: ml/s) which is used in all BPO trials (primary research question).

The IPSS and Qmax are internationally accepted, and the most frequently used primary outcomes in BPO studies, thereby making results from this study comparable to others. There are no core outcomes measures for BPO listed in the COMET Initiative website.

Secondary outcome measures include other well-validated PROs which answer the research questions (section 2 on study objectives) as shown in brackets below:

1. Clavien-Dindo classification of surgical complications [1] (Question 1)
2. Length of hospital stay and transfusion rates (Question 1)
3. ICIQ-MLUTS (for symptom bother) (Questions 3 and 5)
4. International Index of Erectile Function (IIEF) and ICIQ-MLUTSsex (measures of erectile function) (Questions 3 and 5)
5. ICIQ-LUTSqol (condition specific quality of life score) (Questions 3 and 5)
6. EQ-5D-5L (preference based general quality of life measure) (Questions 2 and 3)

7. ICIQ-Satisfaction (measures satisfaction with surgery outcomes) to assess the full impact of the intervention on patients and the NHS (Questions 3 and 4)
8. Resource use for the year following randomization will be collected in order to answer research question 2.
9. Interviews, at 3 to 6 months after surgery, will also be used to answer research questions 4 and 6.

4. Participant entry

4.1 Pre-registration evaluations

4.1.1 Surgeon training prior to the study

ThuVARP uses laser technology to vaporise and resect (remove) 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 clinical co-applicants who will perform both procedures. Therefore, the learning curve for this laser procedure is uniquely short compared to previous laser technologies (e.g. holmium laser) and enhances the potential generalisability of the procedure. Summarising the experience of the Chief Investigator (Mr Hashim Hashim), and other urologists in the UK and Europe, a maximum of 15 ThuVARP laser cases can assure competence in the ThuVARP laser procedure.

All principal investigators will be mentored by the Chief Investigator (CI) and certified by an independent assessor, using standard criteria, before the official study commences. Firstly, surgeons will observe the CI performing one to two cases at Southmead Hospital or their own centre. The CI or PI (already certified as competent with the technique) will then observe the principal investigators in each centre performing 2-5 cases during site visits. The surgeons will then perform 5-10 cases without supervision, following their respective Trust's clinical governance and audit guidelines. Competency will be assessed with the Intercollegiate Surgical Curriculum Programme work-based assessments (ISCP-WBA) by an independent assessor. If competency is not achieved at that stage, then further cases will be observed and training provided by the CI until the competency criteria are met.

A final assessment will be made prior to commencing trial procedures when an independent urological surgeon, experienced in the ThuVARP technique, will observe one final procedure to ensure that the learning curve has been overcome. If the surgeon is still not over the learning curve, then they will perform further procedures with training provided until they have achieved competency as assessed by the ISCP process.

Principal investigators may also train additional surgeons at their site in the laser technique, as per the procedure described above, in order for them to partake in the study. All surgeons will have their competency verified by the independent assessor.

The time taken and the expenses incurred by the surgeons during this process will also be documented in order to obtain an estimate of the training cost associated with the introduction of the ThuVARP laser procedure.

4.1.2 Recruitment and consent

All eligible men referred for consideration of BPO surgery will be identified by the consultant, dedicated research nurse, or designated team member during patients' clinical appointments or from waiting lists for BPO surgery. The Consultant or Research Nurse will introduce the study to the patients at their clinical appointment or by telephone. If the patient expresses interest in the study further details will be provided to the patient by means of the Patient Information Sheet (PIS) and Surgical Information Sheet (SIS). Men contacted by telephone will be asked if they are happy to receive the study information materials by post, and to receive a follow-up telephone call from the Consultant or Research Nurse. Eligible men who cannot be contacted by telephone will receive a brief letter informing them they are eligible for a research study at their hospital. The letter will invite them to telephone the Research Nurse, or to request a telephone call by returning the reply-slip, to find out more. If interest is shown during the telephone call study information materials will be sent out by post and followed-up with a telephone call from the Research Nurse.

The contact details of all interested patients, collected by other team members, will be passed on to the study research nurse. If the patient agrees to the study then arrangements will be made for assessment, counselling and consenting. At the patients' next clinical appointment, or a study-specific appointment, the consultant, dedicated research nurse or designated team member will go through the contents of the PIS and SIS with them and will answer any questions they may have. If the patient is happy to take part in the study the study team member will read through the consent form and ask the patient to put their initials into boxes against statements they agree to and then to sign and date the document. The study team member will add their name and signature at the bottom to confirm their involvement with the consent.

The Patient Information Sheet and the consent form will all refer to the possibility of long-term follow-up and being contacted about other research if the man is willing.

Men who are not willing to be randomised, but who would otherwise be eligible, will be asked to consent to being contacted in the future about other research (e.g. to explore reasons for non-randomisation), and in the future (e.g. for long-term follow-up).

All men who enter the study will be logged with the central trial office and given a unique study number. The participant's General Practitioner (GP) will be informed about each individual patient entered into the trial. Hospital staff will be informed about the study by the Principal Investigator and the research nurse, so that they can answer queries from participants and their relatives.

4.2 Study participants

4.2.1 Inclusion criteria

As this is a pragmatic trial, it will include men 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.

4.2.2 Exclusion criteria

Exclusion criteria include:

- 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.

4.3 Withdrawal criteria

Participants will remain on the trial unless they choose to withdraw or if they are unable to continue for a clinical reason. If a participant withdraws consent, 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.

5. Randomisation and blinding

5.1 Randomisation

Participants will be randomly allocated to treatment arms using an automated web/telephone randomisation system provided by the BRTC. This will take place in the anaesthetic room when the patient is anaesthetised.

Randomisation will be stratified by centre and whether the patient was eligible due to bothersome LUTS or urinary retention.

5.2 Blinding

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.

Participants will be 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 anticipate that some men will ask for, or discover, their allocation at some point during the study and we will ask them to reveal when and how they became aware of this in the 12 month follow-up questionnaire.

Participants will be informed of the type of BPO surgery they received by letter after receipt of their 12-month follow-up questionnaires and bladder diary, or 1 month after they have received a reminder letter for these. As a goodwill gesture UNBLOCS hospital staff will have the option to telephone participants to tell them their allocation and to thank them for taking part in the study.

6. Adverse events and breaches of GCP or Protocol

6.1 Definitions of adverse events

6.1.1 Adverse event (AE)

An AE includes any untoward medical occurrence in a study participant. An AE does not necessarily have to have a causal relationship with the study treatment. In all instances it will be up to the physicians responsible for the participants' care to determine whether the person's change in health is related to the trial.

Adverse events are not continuous and persistent disease or symptoms, present before the trial, which fail to progress; signs or symptoms of the disease being studied (in this case BPO); or treatment failure.

For the UNBLOCS Study, pre-planned hospitalisation or elective procedures e.g. for pre-existing conditions which have not worsened does not constitute an adverse event. However, any hospitalisation of a pre-existing condition resulting from worsening, or elective procedures booked after the patient has signed the consent form would constitute an adverse event.

6.1.2 Serious Adverse Event (SAE)

An SAE includes any untoward and unexpected medical occurrence or effect that:

- Results in death of the participant
- Is life-threatening: the term "life threatening" refers to an event in which the participant was at 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.
- Requires hospitalisation, or prolongation of existing in-patients hospitalisation
- Results in persistent or significant disability or incapacity

Medical judgment will be exercised in deciding whether an AE is serious in other situations.

Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definitions above, should also be considered serious.

6.1.3 Expected, related adverse events

Within UNBLOCS, an adverse event is defined as 'related' if it occurs as a result of a procedure required by the protocol, whether or not this procedure is the specific intervention under investigation or whether or not it would have been administered outside the study as normal care.

The following events can be expected during/after any surgery or urogenital surgery:

- anaesthetic complications
- wound infection
- other infection (sepsis, septicaemia, abscess)
- new urinary tract symptoms
- new sexual problems
- death

The table below describes the complication rates summarised from the literature for TURP and ThuVARP.

Complication	TURP (%)	ThuVARP (%)
Capsular perforation	0.9 – 10	n/a
TUR-syndrome	0 – 2.8	0
Clot retention	1.3 – 11	n/a
Transfusion	0 – 22	0 – 0.8
Urinary tract infection	1.7 – 23	3.3 – 11.1
Urosepsis	0 – 3	1.7
Failure to void	3 – 7.1	2.6
Retrograde ejaculation	53 – 75	55
Erectile dysfunction	3.4 – 32	3.8
Stress Incontinence	<1	0
Urethral stricture	2.2 - 9.8	1.9
Bladder neck stenosis	0.3 - 9.2	0
Re-treatment	3 – 5	2.6
Mortality	<1%	0

6.2 Reporting procedures for adverse events

Within UNBLOCS, all adverse events will be recorded on the Adverse Event Form, whether originally notified on a CRF, participant questionnaires or by other means. In addition all deaths with any cause (related to the trial or otherwise) will be recorded on the adverse event form.

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

6.2.1 Non serious adverse events

All such events, whether expected or not, should be recorded using the Adverse Events form.

6.2.2 Serious adverse events

A Serious Adverse Events form should be completed and uploaded to the secure UNBLOCS file relocation service. This should be followed up by a phone call if receipt is not confirmed. The Trial Manager will inform the CI and Sponsor. If, in the opinion of the local PI and the CI, the event is confirmed as being serious, related to treatment and unexpected, the CI or Trial Manager will notify the sponsor within 24 hours of receiving the AE notification. The sponsor will provide an assessment of the SAE. The CI (or Trial Manager) will report any related and unexpected SAEs to the main REC and the DMC within 15 days of the CI becoming aware of it.

All related Adverse Events will be summarised and reported to the Ethics Committee, the Funder and the Trial Steering Committee in their regular progress reports. Complication rates will be recorded and classified using the internationally accepted Clavien-Dindo classification in trial CRFs [1].

Contact details for reporting SAEs:

jo.worthington@bristol.ac.uk (Trial Manager), hilary.taylor@bristol.ac.uk (Trial Research Associate)

6.3 Breaches of Good Clinical Practice (GCP) or the Protocol

It is the responsibility of the CI and PI at each site to ensure that the research study is run in accordance with ICH GCP and the approved study protocol.

All protocol deviations should be reported to allow their potential impact on participant safety and trial data to be assessed, and any appropriate corrective and preventive actions to be taken.

6.3.1 Definitions of breaches of GCP or Protocol

Breach of GCP

Any action that is not in accordance with that outlined by ICH GCP.

Protocol deviation

Any event whereby procedures outlined in the Protocol were not followed or were changed.

Serious breach

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

- the safety or physical or mental integrity of the subjects of the trial, or
- the scientific value of the trial

6.3.2 Documenting and reporting breaches

All incidents of GCP or Protocol breach should be recorded in the Case Report Form (CRF). In addition, a File Note should be created giving brief details of the breach. The File Note should be scanned and an electronic copy placed in the 'Uploads' folder located in the 'SITES' folder on the University network. The hard copy should be filed in the Site File.

Breaches that are suspected to be serious should be reported to the Trials Unit, as above, within 5 days of becoming aware of the breach.

Full details of the procedure for identifying, documenting and reporting breaches can be found in the UNBLOCS Working Practice Guidelines.

7. Assessment and follow-up

7.1 Clinical measures and events

Urinary flow rate (QMAX), post-void residual (PVR) and voided volume (VV) will be measured before surgery in men who are able to void without a catheter. The most recent existing measures can be used if they were performed within 90 days of informed consent. For men who are catheterised at baseline, the most recent available results will be recorded, whether these are from a previous flow test or from measures taken during a trial without catheter (TWOC, within 90 days of informed consent). PVR and VV will be measured post-surgery, and will be performed as trial procedures for UNBLOCS participants at study centres that do not perform them

as part of routine practice. QMAX, PVR and VV will be measured at 3 and 12 months post-surgery.[1] These follow-up flow measures will not be collected if men are catheterised, but TWOC data will be recorded.

Blood parameters will be measured at baseline and post-operatively, including full blood count (FBC) and urea & electrolytes (U&Es) to look at kidney function and hyponatraemia. The blood tests will be carried out as trial procedures for UNBLOCS participants at study centres that do not perform them as routine practice. Prostate size will be measured by a Digital Rectal Examination prior to surgery, whilst the patient is under anaesthetic. The study nurse will also complete the Charlson Comorbidity Index, and record details of the patient's Body Mass Index, urinalysis results, any antiplatelet or anticoagulant medication and ASA physical status classification prior to surgery. Complication rates will be recorded and classified using the internationally accepted Clavien-Dindo classification. The study nurse will complete a case report form at the time of surgery providing details of the operative procedures, complications and resource use in hospital.

7.2 Patient reported outcomes

Participants will receive the UNBLOCS Symptoms/Surgery Questionnaire at baseline in clinic, 6 weeks post-surgery (by post), and at 3 and 12 months[1] post-surgery in clinic (with the option to take home and return in pre-paid envelope if preferred). The questionnaire contains questions from standardised outcome instruments for urinary and sexual symptoms (listed in the table in section 7.6) and the baseline questionnaire has versions for men who are using a catheter and those who are not (see section 7.7 for questionnaire procedures for catheterised men). Participants who are catheterised at the time of the 3 or 12 months questionnaires will be instructed to only answer the questions that they feel able to. The Bladder Diary will be given to participants at their baseline clinic and at their 3 and 12 months clinics if they do not require a catheter to void at the time. To increase participant privacy, each questionnaire will be presented to the participant with an envelope and the participant will be instructed to seal the questionnaire inside before returning it to the Research Nurse. The Bladder Diary is used to record fluid intake, frequency and volume of micturition and bladder sensation and use of pads over three days, and is returned in a pre-paid envelope. We will attempt to reduce attrition by sending participants a single reminder if a questionnaire is overdue. This reminder will take the form of a letter, phone call, email or text message as appropriate. In addition, we will reimburse travel costs.

7.3 Economic data collection

On discharge from hospital, and at 3 months follow-up the patients will be given a study designed Resource Use Log (RUL) to be used as an aide memoire in which to record NHS and private community based healthcare use, other NHS hospital health care use, medications, social service resource use in addition to travel, time off work/usual activities and any other expenses resulting from their treatment [10]. These logs will reflect the design of the 3 month and 12 month UNBLOCS Resource Use questionnaire. At 3 months and 12 months follow-up[1], participants will be able to use the information from the RUL in order to complete the UNBLOCS Resource Use Questionnaire which they will take home from clinic, or receive by post, along with a pre-paid return envelope. The EQ-5D-5L will be used to calculate quality adjusted life years (QALYs). The new 5-level EQ-5D will be used in preference to the 3-level one, owing to its improved discriminatory power [11].

7.4 Qualitative data collection

The main aims of the qualitative component, which will be investigated with in-depth semi-structured interviews with participants at between 3-6 months post-surgery are:

1. To explore patient experiences of ThuVARP and TURP
2. To explore patient-determinants of satisfaction with the two procedures
3. To identify any differences in experience between men presenting with LUTS or urinary retention.

[1] The final patients to be consented at the end of recruitment may have a shortened follow up time for logistical reasons. Approximately 30 patients may have a follow up time of between 10 and 12 months, rather than the full 12 months.

The basis of the interview schedule/topic guide will be focused around these three themes and will be further informed by the literature and clinical experience of the co-applicants but also allowing participants to address issues or concerns of particular relevance to their own experience. Interviews have been targeted at three to six months post-surgery to allow recovery from the operation and return to daily activities whilst also permitting good recall of the experience of the procedures and immediate sequelae.

Participants from both the ThuVARP and TURP intervention arms will be recruited to take part in exploratory interviews. Study participants who provide consent to being approached for qualitative interviews will be purposively selected to represent the two surgical interventions, two presentations for surgery (LUTS and urinary retention) and demographic characteristics such as age. This is included to better understand the differences between the two surgical procedures in terms of the individuals' lived experience. In particular the interview schedule will focus on the immediate experience surrounding surgery and features of the continued recovery and effects on daily life. This is important to capture contextual data to support interpretation and contextualisation of the trial quantitative outcomes.

Participants will also be asked to articulate what their expectations of surgery were prior to the procedure and upon which factors they judged their perceived satisfaction, or dissatisfaction subsequent to the operation and whether this was a dynamic or static decision that altered during the recovery period. This aspect of the investigation will focus on capturing both clinical and non-clinical determinants of satisfaction which will be linked to the quantitative analyses for interpreting the outcomes e.g. quality of life.

7.5 Case report forms (CRFs)

The research nurse or urologist will complete CRFs with the following content:

7.5.1 Baseline CRF

To be completed at the patient's baseline clinic appointment

- Patient contact details
- Patient date of birth and ethnicity
- Record of other diagnostic assessments (invasive urodynamics and transrectal ultrasound)
- Prostate-Specific Antigen (PSA) results (if available)
- GP contact details
- Charlson Comorbidity Index data
- Blood parameters
- Digital Rectal Examination (DRE) data (if available)
- Urine flow rate (Qmax), post void residual volume (PVR) and voided volume (VV) data
- Details of catheterisation

7.5.2 Perioperative CRF

To be completed during the patient's TURP/ThuVARP operation

- Perioperative data including date of admission and operation
- ASA physical status classification
- DRE results
- Resection weight
- Resource use
- Operative procedures and theatre time
- Details of urinalysis
- Details of antiplatelet or anticoagulant medication
- Body Mass Index (BMI)
- Complications
- Details of catheterisation

7.5.3 Postoperative CRF

To be completed during the patient's post-operative inpatient stay

- Post void residual volume (PVR)) and voided volume (VV) data
- Date of discharge
- Details of catheterisation
- Blood parameters
- Details of irrigation
- Complications

Details of when antiplatelet or anticoagulant

- Resource use

medication will be restarted

7.5.4 Trial without catheter sheet (TWOC Sheet)

To be completed for all TWOCs the patient has post-operatively, whether as an inpatient or outpatient

- Date/time of TWOC
- VV and PVR
- Details of recatheterisation

7.5.5 Return to Theatre CRF

To be completed for any returns to theatre the patient has during their original inpatient stay for their TURP/ThuVARP procedure

- Reason for return to theatre
- Staff present
- Procedure and recovery times

7.5.6 Post-op Ward Stay Sheet

- To be completed for all wards the patients stays on during their original inpatient stay for their TURP/ThuVARP procedureDates of stay on ward
- Type of ward
- Visiting staff

7.5.4 Three months and 12 months post-surgery

- Urine flow rate (Qmax), post void residual volume (PVR) and voided volume (VV) data
- Complications
- Prostate histology
- Details of catheterisation
- Resource use

7.5.5 Medical record abstraction

At 12 months follow-up in-patient stays, out-patient visits and procedures occurring in the initial treating hospitals will be abstracted from the patients' medical records.

7.6 Measurement of outcomes: components and timing

Outcome measurement	Baseline	Peri-operative	Post-operative	6 weeks	3 months	12 months
Case report form (CRF)	X	X	X		X	X
ICIQ-Bladder diary	X				X	X
Maximum urine flow rate (QMAX)	X				X	X
Post-void residual (PVR)	X		X		X	X
Voided Volume (VV)	X		X		X	X
Full blood count (FBC)	X		X			
Urea & Electrolytes (U&Es)	X		X			
Charlson Comorbidity Index	X					
Digital Rectal Examination	X	X				
Antiplatelet/anticoagulant medication		X	X			
Urinalysis		X				
IPSS	X			X	X	X
ICIQ-MLUTS	X			X	X	X
ICIQ-MLUTSsex	X			X	X	X
IIEF	X			X	X	X
ICIQ-LUTSqol	X			X	X	X
EQ-5D-5L	X			X	X	X
ICIQ-satisfaction				X	X	X
Body Mass Index		X				
ASA physical status classification		X				
Operative time and procedures		X				
Resection weight		X				
Irrigation			X			
Catheterisation		X	X		X	
Length of hospital stay			X			
Complications		X	X		X	X
Interviews					X	
Resource use questionnaire					X	X

7.7 Procedures for catheterised participants

Some measures will be collected differently for participants who require a catheter to void, at the measurement time-point. Outcome measurements that differ for these men are summarised in the table below. Other outcomes remain the same as for non-catheterised participants.

Baseline

The most recent available urine flow results will be collected from clinical notes at baseline, whether these are from a flow test pre-catheterisation or from a trial without catheter. A separate version of the Baseline Symptom/Surgery questionnaire is available for participants who are catheterised at the time of the measure. These men will be asked to complete the questions on urinary symptoms, sexual function and quality of life in the Baseline Questionnaire by recalling their condition before they were catheterised (with the exception of the EQ-5D-5L which will be answered for their current state of health).

Follow up

Men who are unable to void without a catheter at the time, will not provide flow-test results post-operatively, or at 3 and 12 months follow-up. For the 6 week, 3 month and 12 month questionnaires men who are using a catheter to void will be asked to only answer the questions that they feel able to.

Outcome measurements that differ for patients who are catheterised, at each time-point					
Outcome measurement	Baseline	Post-operative	6 weeks	3 months	12 months
ICIQ-Bladder diary	X[c]			X[c]	X[c]
Maximum urine flow rate (QMAX)	X[a]			X[c]	X[c]
Post-void residual (PVR)	X[a]	X[c]		X[c]	X[c]
Voided Volume (VV)	X[a]	X[c]		X[c]	X[c]
IPSS	X[b]		X[d]	X[d]	X[d]
ICIQ-MLUTS	X[b]		X[d]	X[d]	X[d]
ICIQ-MLUTSsex	X[b]		X[d]	X[d]	X[d]
IIEF	X[b]		X[d]	X[d]	X[d]
ICIQ-LUTSqol	X[b]		X[d]	X[d]	X[d]

[a]Most recent available results, from flow test or trial without catheter, collected from notes, for men using a catheter to void.
[b]Patients catheterised at the time of questionnaire asked to recall their condition before they were catheterised.
[c]These measures will not be collected from men who are using a catheter to void, at the time of measurement
[d]Patients who are catheterised at the time of questionnaire will be asked to only answer questions that they feel able to.

8. Data management and security

8.1 Data collection and transportation

All data held in Bristol will conform to the University of Bristol Data Security Policy and in Compliance with the Data Protection Act 1998.

Data collected on paper case report forms at study centres or as questionnaires from participants will be identifiable only by participant study number. This will be transported by post to the UNBLOCS study office at University of Bristol, and stored in a secure locked cabinet in a locked room.

Data obtained by paper will also be entered onto and maintained on an SQL Server database system maintained by University of Bristol Information Services. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to UNBLOCS study staff.

Information capable of identifying participants will not be removed from University of Bristol or clinical centres or made available in any form to those outside the study.

8.2 Qualitative data

Audio recordings made during the interviews will only refer to the participant by their study number. However it is possible that participants may give information from which they could be identified, during the interview. Therefore all audio recordings will be made on encrypted digital recorders, and the files will be deleted from the recorder once they have been uploaded to the server at University of Bristol.

8.3 Retention of data

Patient identification codes will be held by BRTC for 15 years, all other data sources will be stored for 10 years after the close of the study. Personal data (e.g. name and address, or any data from which a participant might be identified) will be withdrawn from the study if this is requested by a participant.

8.4 IT security

All IT systems supported and maintained by the University of Bristol Information Services will have infrastructure including server and server-based applications and desktop system maintenance. All NHS IT systems will be similarly supported. Data is stored centrally on robust data systems with file versioning and recovery and mirroring on a second site. The BRTC Randomisation system infrastructure is also maintained by University Information Services.

8.5 Auditing and inspection

The study may be subject to inspection and audit by North Bristol NHS Trust under their remit as sponsor, and other regulatory bodies, to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8.6 Access to the data

8.6.1 Source data

The PI will allow monitors from the sponsor (NBTR&I), persons responsible for the audit, representatives of the Ethics Committee and of the Regulatory Authorities to have direct access to source data/documents.

8.6.1 Anonymised trial data

The Senior IT Manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses.

9. Statistics and data analysis

9.1 Sample size determination

This study is powered to establish equivalence in clinical improvement. The Chinese trial [7] 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 [12,13].

After considerable discussions between clinicians both inside and outside the trial, we have specified differences of 4 ml/s in QMAX and 2.5 units in IPSS, as demonstrating equivalence (null hypothesis). 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 is 163 patients in each group. Using NQuery Advisor, this will provide 85% power to demonstrate equivalence for IPSS and just over 90% power for Qmax, at a two-sided alpha of 5%. Assuming 20% loss to follow-up following randomisation, it will be necessary to recruit 410 men in total. This loss to follow-up is a conservative estimate from our experience of previous trials. However, we will aim to reduce loss to follow-up through letter, text and telephone reminders to patients.

9.2 Recruitment rates and expected throughput per centre

Each of the centres in the trial performs between 150 and 400 benign prostate surgery per year. Therefore the accrual target of 410 can be achieved within a 15 months recruitment period (months 6-20 inclusive) based on a throughput of approximately 820 eligible patients in 6 centres, assuming 70% are eligible with 50% randomisation (62% in the ProtecT trial [14] between three treatments) and that 50% of eligible patients will be missed in the first month and 50% will be missed in August and December due to staff holidays. We expect that 50% of the remaining eligible patients will be willing to be randomised. Each centre will recruit 4 to 5 men each month, although our prior experience shows that recruitment generally increases over time.

In allowing for loss to follow-up to the 12-month post-procedure assessment, 205 patients will be randomly allocated to each arm of the study. It is likely that near-complete post-operative data will be available for these patients. With a standard deviation for post-surgery serum haemoglobin of approximately 14 g/L (based on 98 patients [15]) 205 patients per arm will give 90% power at the 5% significance level to detect a 4.5 g/L difference in mean serum haemoglobin. The study is consequently sensitive to clinically important differences in post-operative haemoglobin as a safety measure.

This study is powered to establish equivalence in clinical improvement. After extensive discussions we are specifying differences in Qmax and IPSS of no greater than 4 ml/s and 2.5 units respectively, as demonstrating equivalence (null hypothesis).

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 NCRI accredited Bristol Randomised Trials Collaboration (BRTC).

9.3 Primary and secondary analyses

CONSORT guidelines will be followed for the data analysis. As this is a pragmatic trial, the primary comparative analysis will be conducted on an intention-to-treat basis. The primary analysis will employ multi-variable regression to investigate differences in Qmax and IPSS between ThuVARP and TURP at 12 months. Analyses will adjust for stratification variables (including centre) and baseline measurements of the relevant outcome. Baseline comparability of the ThuVARP and TURP groups will be examined, and any important imbalances at randomisation will be adjusted. Observed differences, 95% confidence intervals and p-values will be presented but with emphasis on confidence intervals for the between-group comparisons when considering equivalence. There may be an issue of missing data, and if so, methods of multiple imputation modelling will be employed in a secondary analysis. A full statistical analysis plan will be developed and agreed by the Data Monitoring Committee and Trial Steering Committee prior to undertaking any analyses.

The primary analysis of the primary outcome measures (maximum flow rate and the IPSS PROM) will be intention to treat, as this approach takes full advantage of the random allocation to keep the two study arms comparable at the outset. The concern with this approach is that if some patients receive the other treatment, and not the one they were allocated to, there will be a spurious equivalence in outcome. That is, the outcomes are similar, because there are a proportion of patients in the two arms who are being treated identically. To allow clinicians and policy makers to gauge whether this is a problem with our results, we will present this

intention to- treat analysis with data on those who received their allocated treatments. As randomisation will occur close to the time of surgery, a significant cross-over between treatment groups is thought unlikely.

We will also conduct secondary analyses to assist with the interpretation of the primary result. The exact nature of this secondary analysis will depend on the nature of any non-compliance with allocation. If non-compliance is predominantly patients allocated to ThuVARP actually receiving TURP, then an unbiased estimate of the treatment comparison in patients receiving their allocated treatment can be obtained using the "Complier Average Causal Effect" (CACE) method. If other forms of non-compliance are observed then we will conduct a "per-protocol" analysis based on patients receiving their allocated intervention, and present this with caveats due to the likely bias in the resulting estimates (the comparison is not between the complete randomly allocated groups).

These analyses will be based on multivariable regression models, with the focus being on whether the effect estimates and 95% confidence intervals indicate that clinically significant differences between ThuVARP and TURP are unlikely. In the event of loss to follow up prior to the primary 12-month assessment, secondary analyses will explore how this is affects the primary analysis of observed data. Multiple imputation will be employed, and cautiously interpreted due to the likely Missing Not At Random (MNAR) mechanism resulting from loss to follow-up. Simple imputation will explore the limits of the effect of missing data, by making a range of assumptions about the missing data, e.g. patients drop out when treatment fails or patients drop out because they require no further medical attention.

9.4 Economic data analysis

The trial will include a formal economic evaluation comparing the costs and cost-effectiveness of the interventions from an NHS and broader societal perspective. The cost of the interventions and the use of primary and secondary NHS services by the men, personal and social service costs, costs to the men arising from their treatment (e.g. travel, over the counter medication) and productivity costs, will be estimated through the collection of resource-use data as outlined earlier and the valuation of these data.

Micro-costing of the initial hospital stay will be needed and therefore Trust finance departments of the participating hospitals will be approached in order to value the initial NHS resources used. All other resource use will be valued using routine sources and information from the patients themselves.

The EQ-5D-5L will be administered at baseline and at 6 weeks, 3 and 12 months after the operation. If available at the time of analysis, the societal utility tariffs, derived from the on-going valuation studies, associated with the answers to this questionnaire will allow the creation of QALYs for these men. Otherwise the response mapping approach will be used.

The cost-effectiveness analysis will take a societal perspective with NHS costs reported separately. Only resources used in relation to the treatment of LUTS, or urinary retention secondary to BPO, will be measured from randomisation at the time of surgery, to 12 months follow-up. Details of initial hospital stay resource use e.g. operation duration; operating staff; consumables; the time spent in recovery; length of stay on different wards; overall length of stay and treatment for complications, will be collected on study designed case report forms by the research nurse at the time of the inpatient/day-case stay for the initial surgery. At 12 months follow-up, any subsequent in-patient stays, out-patient visits and procedures occurring in the initial treating hospitals, will be abstracted from the patients' medical records.

Initially regression techniques adjusting for pre-specified baseline characteristics, randomisation variables and a centre effect will be used to evaluate the difference in costs. Boot-strapped confidence intervals will be used, given the potential non-normality of the cost data. The same model will be used to evaluate the difference in QALYs. The differences in terms of the two primary outcomes will be evaluated according to the statistical analysis plan.

If no arm is dominant i.e. cheaper and more effective, then incremental cost-effectiveness ratios will be calculated. It will also be possible when comparing the difference in costs and the difference in QALYs to use

the net benefit framework over a range of values for the QALY. This will facilitate the use of regression modelling to adjust for pre-specified baseline characteristics, randomisation variables and centre effects. Uncertainty as stated before will be addressed using cost-effectiveness acceptability curves and sensitivity analyses. One aspect of uncertainty is likely to be that of missing data. As with the main analysis, a pre-specified analysis plan will be created in which the plausible assumptions about missing data will be created and tested using these assumptions within the sensitivity analyses.

Additionally the costs of surgeon training for the ThuVARP laser technique will be estimated. This will be reported to allow policy makers to more accurately estimate the costs of service reconfiguration if the ThuVARP laser is shown to be equivalent to the TURP. These costs will also be incorporated in one of the sensitivity analyses, alongside an estimate of the cost of surgeon training for the TURP.

No modelling has been specified within this evaluation, as the work is seen as a definitive trial, and experience has shown that most uncertainty in relation to cost differences will be captured within the first 12 months, the duration of this trial.

9.5 Qualitative data analysis

A standardised approach will be employed to explore the above areas in accordance with published qualitative research methods. Face-to-face patient interviews will be conducted where possible, with telephone interviews included for other study sites, which will be carried out by an experienced qualitative researcher. Interviews will be digitally recorded, transcribed verbatim and uploaded into a qualitative software package to aid data management (NVivo). Analyses will be conducted by the qualitative researcher according to the principles of thematic content analysis. Recordings will be listened to and transcripts read and re-read for familiarisation. Segments of text will be 'coded' by assigning descriptive labels. Codes will be grouped on the basis of shared properties to create themes, and coded transcripts will then be examined and compared to inductively refine and delineate themes (constant comparison). A subset of interviews will be independently analysed by a second study researcher and coding discrepancies discussed to maximise rigour and reliability. Plausibility of data interpretation will be further discussed between the study team, including the clinical co-applicants, throughout the analyses. Descriptive summary accounts of the interviews will be prepared.

Theoretical purposive (non-probability) sampling will be used, where explanations, developing to describe the data during analyses, guide further sampling and data collection. Maximum variation sampling will also ensure the diverse characteristics of the population are sampled (e.g. participants varying in age, clinical history and surgery received). Sampling and analyses will continue in iterative cycles until no new themes are emerging and established themes cease evolving: data saturation. It is anticipated that approximately 30-40 participants will be required, with up to 20 per procedure to allow for sampling of those with LUTS and urinary retention as the reason for their treatment.

10. Project timetable and milestones

Study start is 1 January 2014. The study duration of 49 months comprises a set-up/site initiation period of 5 months, 30 months recruitment, 11 months to complete follow-up and 3 months data analysis and dissemination

10.1 Overall project timetable

Milestone	Months
Completing multi-centre research ethics and central Research & Development approvals, set-up office, construct database, assemble team, and establish all 6 centres	1-5
Recruit and randomise 410 participants	6-35
Follow-up at 6 weeks, 3 months and 12 months after surgery	7-46
Complete data collection, analysis and dissemination	47-49

11. Organisation

11.1 Local organisation in centres

11.1.1 Lead Urologist

Each collaborating centre will identify a Lead Urologist who will be the point of contact for that centre. The responsibilities of this person will be to:

- establish the study locally (for example, by getting agreement from clinical colleagues; facilitate local regulatory approvals; identify, appoint and train a local Research Nurse; and inform all relevant local staff about the study (e.g. other consultant urologists, junior medical staff, secretaries, ward staff));
- take responsibility for clinical aspects of the study locally (for example if any particular concerns occur);
- identify men who are eligible to participate in the trial, explain the different surgery options to them, and ensure that study documentation has been provided and that informed consent has been obtained;
- notify the Study Office of any unexpected clinical events which might be related to trial participation;
- provide support, training and supervision for the local Research Nurse(s);
- represent the centre at the collaborators' meetings.

11.1.2 Local Research Nurse

Each collaborating centre will appoint a local Research Nurse to organise the day to day recruitment of men to the trial. The responsibilities of this person will be to:

- keep regular contact with the local Lead Urologist, with notification of any problem or unexpected development;
- maintain regular contact with the UNBLOCS Study Office;
- keep local staff informed of progress in the trial;
- contact potential participants by: providing the Patient Information Sheet to men being admitted electively for benign prostate surgery; identifying any eligible men at pre-assessment clinics or on the ward while they are in hospital for their surgery; explain the study and the potential for participation in a trial if they are eligible; explaining what is intended by research access to their NHS data; and describing the possibility of long-term follow up and participation in other research;

- obtain the man's written consent;
- keep a log of whether eligible men are recruited or not (with reasons for non-participation);
- collect baseline data describing the men, log this information in the web-based UNBLOCS database and send paper copies to the Study Office along with the original signed consent forms;
- use this information to randomise the men using the web-based UNBLOCS database or telephone;
- ensure operative and postoperative data are collected and recorded in the UNBLOCS database, and send paper copies to the Study Office;
- file relevant study documentation (e.g. consent forms) in the man's medical records and ensure full and accurate records are maintained in accordance with ICH Good Clinical Practice Guidelines;
- organise and supervise alternative recruiters in case of holiday or absence;
- represent the centre at the collaborators' meetings.

11.2 Patient Representation

Two patient representatives are members of the UNBLOCS Trial Steering Committee and provide the trial with input and guidance from a patient perspective. Wider patient consultation was and will continue to be sought as required, including advice on all patient documentation.

11.3 Study co-ordination in Bristol (BRTC)

The Study Office will be based in the BRTC within the School of Social & Community Medicine at the University of Bristol, and will provide day to day support for the clinical centres. The Trial Manager based at the BRTC will take responsibility for the day to day supervision of study activities. As per BRTC's business and costing model, the Senior IT manager will oversee all IT aspects of the study, while the Senior Trials Manager will provide mentoring and guidance to the trial manager and advice to the team on generic coordination issues. The UNBLOCS Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting.

11.4 Project Management Group (PMG)

The study will be supervised by a PMG. The chair of this group will be Mr Hashim Hashim (Chief Investigator) and will consist of grant holders, and representatives from the Study Office. The PMG will meet monthly for the first 6 months from study start and quarterly thereafter. In addition, the PMG will also be represented at the Trial Steering Committee meetings.

11.5 Trial Steering Committee (TSC)

The role of the TSC is to monitor and supervise the progress of the trial. The membership will consist of an independent chair (Prof. Tom McNicholas), together with at least two other independent members, and the trial manager and the Chief Investigator (CI: Mr Hashim Hashim) will also attend. The TSC will also comprise of two patient representatives. Observers may also attend, as may other members of the Project Management Group (PMG) or members of other professional bodies at the invitation of the Chair.

11.6 Data Monitoring Committee (DMC)

The DMC will also have an independent chair, and will monitor accumulating trial data during the course of the trial and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or closure of the trial. It is anticipated that both the TSC and the DMC would meet twice a year. The CI, all PIs, study co-ordinators, research nurses, and BRTC personnel will have undertaken the mandatory Good Clinical Practice (GCP) training.

12. Regulatory issues

12.1 Ethics approval

The Chief Investigator has obtained approval from the South Central - Hampshire B Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study from that Trust. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

We believe this study does not pose any specific risks to individual participants beyond those of any surgery, nor does it raise any extraordinary ethical issues.

12.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. 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.

Men who are not willing to be randomised, but who would otherwise be eligible, will be asked to consent to being contacted for other research (e.g. to explore reasons for non-randomisation), and being contacted in the future (e.g. for long-term follow-up).

A standardised Surgical Information Sheet will be used to provide specific clinical information for men about the two surgical options, including known complications.

12.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

12.4 Indemnity

The necessary trial insurance is provided by the sponsor. North Bristol NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this trial. The Patient Information Sheet provides a statement regarding indemnity for negligent and non-negligent harm.

12.5 Sponsor

North Bristol NHS Trust will act as the Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in this trial.

12.6 Funding

The National Institute for Health and Research, Health Technology Assessment programme are funding this study (ref. 12/35/15).

13. Publication policy

The success of the study depends entirely on the wholehearted collaboration of a large number of men undergoing BPO surgery, as well as their nurses and doctors. For this reason, chief credit for the study will be given, not to the committees or central organisers, but to all those who have collaborated in the study. The results of the study will be reported first to study collaborators. The main report will be drafted by the Project

Management Group and circulated to all clinical collaborators for comment. The final version will be agreed by the Steering Committee before submission for publication, on behalf of all the UNBLOCS collaborators.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior agreement from the Project Management Group.

We intend to maintain interest in the study by publication of UNBLOCS newsletters at intervals for participants, staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final UNBLOCS Newsletter to all involved in the trial.

The main forms of dissemination will be through the academic press, HTA monograph, guidelines and workshops for clinical staff and by lay summaries on websites and other more accessible forms for patients. All participants will be offered a lay summary of the main findings of the study. Dissemination to clinicians will be through papers in major urology journals and conferences (e.g. the European Association of Urology), workshops and presentations to national meetings e.g. the British Association of Urological Surgeons (BAUS) which is the specialist body with the responsibility for guiding clinical practice, policy matters, research priorities, governance and training in matters related to male lower urinary tract symptoms. BAUS is well placed to implement the findings by informing NHS policy (NICE) and dissemination of evidence-based clinical practice to its members. The Patient Panel working with the trial will assist in the best methods to disseminate the results to patients, including interacting with the relevant charities in this area.

The UNBLOCS trial would also be part of the portfolio of the new Royal College of Surgeons of England Surgical Centre in Bristol so will be used as a platform for clinical trial training for new surgeon investigators, as well as the opportunity to conduct methodological research in surgical trials which would be disseminated by the surgical centre through workshops and publications.

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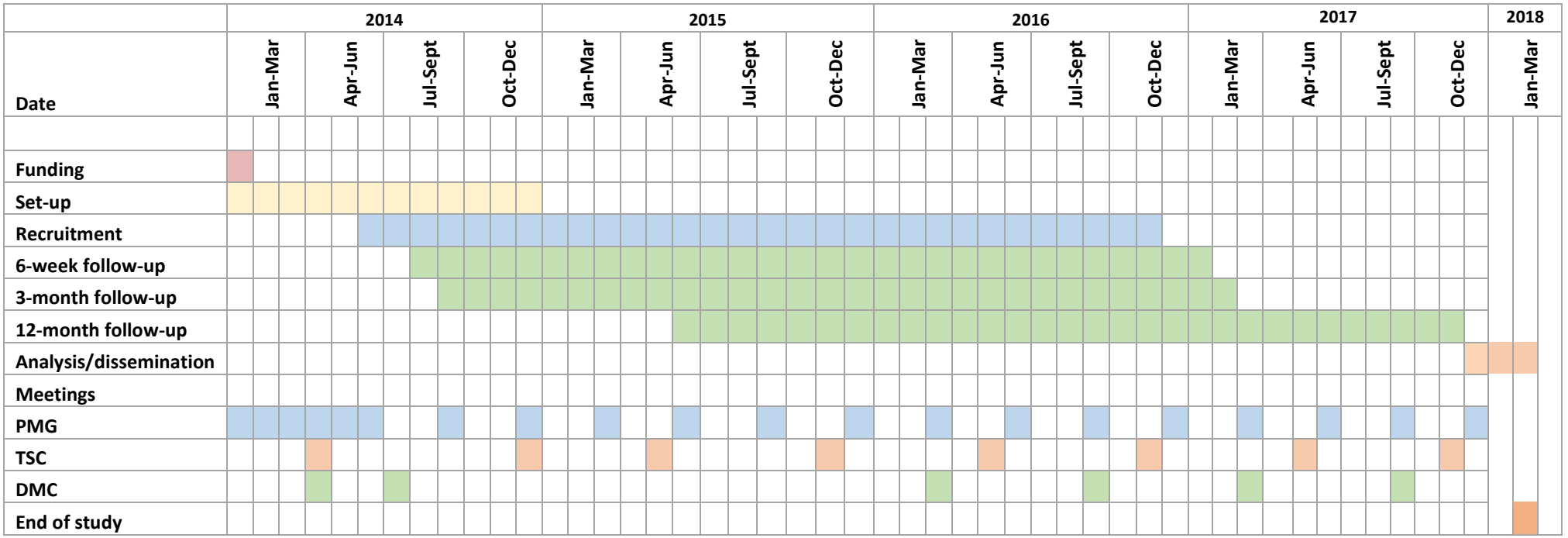
15. Appendix 1. UNBLOCS gantt chart



PMG: Project Management Group
TSC: Trial Steering Committee
DMC: Data Management Committee