Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods

Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) for diagnosis and management of bladder outlet obstruction in men

Protocol

Version 4

29/09/2016

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Name & Role ***Date*** ***Signature***

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This protocol describes the UPSTREAM 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.

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Protocol summary

Questions addressed

- Is a care pathway excluding invasive urodynamics no worse for men in terms of symptom outcome than one in which it is included?
- Does the inclusion of invasive urodynamics reduce the rate of bladder outlet surgery?

Considered for entry

Men with bothersome voiding LUTS and suspected bladder outlet obstruction (BOO) for whom surgeons would potentially offer surgery.

Population

Men with bothersome voiding LUTS and suspected bladder outlet obstruction.

Trial entry

Eligible and consenting men. Consent will be obtained from men after written and oral information has been provided.

Interventions

Treatment decisions for BOO based on:

- Non-urodynamic assessment, based on voiding symptoms and a reduced urinary flow rate (usual care)
- Urodynamics in addition to the non-urodynamic assessments (usual care plus urodynamic assessment)

Outcome assessments

- Questionnaires at 6, 12 and 18 months after randomisation;
- Bladder diary and urinary flow rate at 18 months;
- Health care utilisation questions at 6, 12 and 18 months;
- (For men who have surgery): urinary flow rate at 4 months after surgery.

Co-ordination

- Local: by local lead Urologist and Research Nurse.
- Central: by Study Office in Bristol.
- Overall: by the Project Management Group and overseen by the Trial Steering Committee and the Data Monitoring Committee.

Funding

National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, Health Technology Assessment (NETSCC HTA) Programme: Reference Number 12/140/01

Ethics committee details

South Central – Oxford B, 14/SC/0237

Sponsor details

North Bristol NHS Trust; Reference Number: R&I 3250

Study registration

controlled-trials.com: ISRCTN56164274

Dates

- Start date: 1st April 2014
- Planned end date: 30th September 2018
- Planned reporting date: 18th October 2018

Summary in plain English

Some men develop difficulty passing urine (voiding) as they age. This may be because an enlarged prostate gland (which sits round the base of the bladder) narrows the bladder outlet (urethra) or because the bladder becomes less able to contract. Prostate surgery is more likely to help symptoms in the first group, while the second group may have no improvement after surgery, while being exposed to risk of complications of surgery.

Invasive urodynamics involves putting a tube (catheter) into the bladder via the penis, and another into the rectum, to measure bladder and abdominal pressures while the bladder is filled with a sterile fluid. Invasive urodynamics can measure bladder pressures during filling and voiding, and bladder outlet obstruction pressures. The procedure is considered safe, but some men find it uncomfortable or undignified, and a few develop urine infection afterwards. We think that it could be useful to select the men who should and should not have surgery. However, no studies have been conducted so far to tell us if this is true: UPSTREAM is designed to find out if the invasive tests are worthwhile.

UPSTREAM is a randomised controlled trial in men who have bothersome difficulty passing urine, and who are seeking further treatment, which may include having surgery for the symptoms. The group studied will be men who continue to be bothered by difficulty passing urine, despite initial treatment such as drugs, where symptoms are thought to be due to bladder outlet obstruction. The men will be assigned at random to either urodynamic tests as well as the standard non-invasive tests ("Urodynamics") or to the routine standard tests ("Non-urodynamic assessment" control arm) alone. Routine standard tests include asking men to complete a questionnaire (the International Prostate Symptom Score (IPSS)) and a bladder diary, carrying out flow rate testing, conducting a physical examination, and checking the urine for infection. Some surgeons also use "discretionary tests" such as the PSA cancer-screening blood test.

The following men will be invited to participate (inclusion criterion):

- Men seeking further treatment for their bothersome lower urinary tract symptoms (LUTS) which may include surgery

Men will not be invited to participate (exclusion criteria) if they:

- are unable to pass urine without a catheter (urinary retention) (excluding clean intermittent self catheterisation [CISC] after void to empty)
- have a relevant neurological disease, such as a stroke, multiple sclerosis, Parkinson's disease, or Spina bifida (diabetes mellitus is not an exclusion criterion unless it is causing diabetic neuropathy)
- are undergoing treatment for prostate or bladder cancer (including AS for low grade/stage transitional cell cancer [TCC])
- have previously had prostate surgery
- are not medically fit for surgery, or are unable to complete outcome assessments
- do not consent to be assigned at random to one of the pathways and/or are not willing or able to comply with essential study procedures

We will compare the two methods of investigation by finding out whether the men had similar relief of their symptoms, by measuring the change in the prostate symptom score (IPSS) in the two groups at 18 months after randomisation.

We will also look at the following secondary outcomes:

- Whether the invasive tests changed the decision for surgery in some of the men (how many men had surgery in each of the two groups?)
- The cost-effectiveness of the two management pathways
- Adverse effects of (a) the tests and (b) the treatments at 6, 12 & 18 months (e.g. urinary infection, urinary retention)

- Urinary symptoms and quality of life at 6, 12 & 18 months, using the International Consultation on Incontinence Questionnaires (ICIQ) and the Male Lower Urinary Tract Symptoms questionnaire (ICIQ-MLUTS)
- Sexual function, using the ICIQ-MLUTS sex questionnaire
- Satisfaction with urodynamic testing, using the ICIQ-UDS-S questionnaire
- The maximum urinary flow rate (Qmax) at 18 months
- Health outcomes, using the EQ-5D-5L questionnaire
- Qualitative interviewing will explore user acceptability of urodynamics and influences on decisions made by the participating men and the surgeons

We worked out that 400 men would need to be recruited to each arm of the trial to detect a difference of one point on the IPSS, which is the main clinical measure of the symptoms. Allowing for men who do not want to participate, and who drop out once the trial starts, we would need to approach 3800 men during an 18 month recruitment period to reach the required number in each arm.

The study will be supported by a Trial Steering Committee, a Patient Involvement Panel and a Data Monitoring Committee. The information will be important for men trying to decide on management of their symptoms, for the doctors advising them, and for the NHS in ensuring best use is made of resources for this common problem.

Glossary of abbreviations

AE	Adverse Event
BAUS	British Association of Urological Surgeons
BCI	Bladder contractility index
BOO	Bladder outlet obstruction
BOOI	Bladder outlet obstruction index
BPO	Benign prostatic obstruction
BRTC	Bristol Randomised Trials Collaboration
CI	Chief Investigator
CISC	Clean intermittent self catheterisation
CG	Clinical guideline
CRF	Case report forms
CTU	Clinical Trials Unit
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
GP	General Practitioner
HES	Hospital Episodes Statistics
HTA	Health Technology Assessment
ICIQ-DUA	International Consultation on Incontinence Questionnaire- Detrusor underactivity
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
ICIQ-UDS-S	ICIQ urodynamics satisfaction
IPSS	International prostate symptom score
ISRCTN	International Standard Randomised Controlled Trial Number
LUTD	Lower urinary tract dysfunction
LUTS	Lower urinary tract symptoms

NBT	North Bristol NHS Trust
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
OAB	Overactive bladder syndrome
PI	Principal Investigator
PMG	Project Management Group
PP	Patient Panel
PROs	Patient reported outcomes
PSA	Prostate specific antigen
PVR	Post-void residual
QALY	Quality adjusted life years
Qmax	Maximum urinary flow rate
RCT	Randomised controlled trial
R&D	Research and Development
R&I	Research and Innovation
SD	Standard deviation
SAE	Serious Adverse Event
SSA	Site Specific Assessment
SUSAR	Suspected unexpected serious adverse reaction
TSC	Trial Steering Committee
TURP	Transurethral resection of prostate
U&Es	Urea & electrolytes
UK	United Kingdom
UAR	Unexpected adverse reaction
UDS	Urodynamic studies
VV	Voided volume

Keywords

Invasive Urodynamics, Cystometry, TURP, Prostate, Benign, Obstruction, Surgery

Study summary

Title

"Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) for diagnosis and management of bladder outlet obstruction in men"

A randomised controlled trial to determine the clinical and cost effectiveness of invasive urodynamic studies for diagnosis and management of bladder outlet obstruction in men.

Acronym: Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods – UPSTREAM
Short title: Assessment methods for prostate surgery

Design

Randomised controlled parallel-group trial

Aims

The aim of the UPSTREAM trial is to determine whether a care pathway not including invasive urodynamics is no worse for men in terms of symptom outcome than one in which it is included, at 18 months after randomisation. We will also establish whether inclusion of invasive urodynamics reduces rates of bladder outlet surgery as a main secondary outcome.

Primary outcome measure

This primary clinical outcome will be measured with the widely-used patient reported outcome, the International Prostate Symptom Score (IPSS) at 18 months post-randomisation.

Secondary outcome measures

- Surgery rate (the relative proportion of men in each group having surgery up to 18 months after randomisation).
- Cost-effectiveness analyses from the perspectives of the NHS, Personal Social Services and patients. Subsequent need for surgery will be recorded.
- Adverse events of testing and treatment (e.g. infection, urinary retention).
- Measures from the International Consultation on Incontinence Questionnaires (ICIQ) 32 will be used, giving sensitive and comprehensive assessment of LUTS severity/ bother, sexual function, quality of life and satisfaction with urodynamic testing:
    - ICIQ Male LUTS (ICIQ-MLUTS)
    - ICIQ sexual function in Male LUTS (ICIQ-MLUTS-sex)
    - ICIQ urodynamics satisfaction (ICIQ-UDS-S)
- Maximum urinary flow rate (Qmax) at 18 months. In men undergoing surgery in both arms, an additional Qmax measure at 4 months after operation will be used as a quality measure for surgery.
- The EQ-5D-5L will be used to provide the quality of life weights used to calculate Quality Adjusted Life Years (QALYs).
- Qualitative interviewing will explore user acceptability and influences on decisions made by the participating men and the surgeons.

All men will be invited to consent to long term follow up, including use of computerised NHS records, HES data and other routine data sources.

Population

Adult men, including and over, the age of 18 years

Eligibility

Inclusion criteria

- Men seeking further treatment for their bothersome lower urinary tract symptoms (LUTS) which may include surgery

Exclusion criteria

Patients who:

- are unable to pass urine without a catheter (urinary retention) (excluding CISC after void to empty)
- have a relevant neurological disease such as stroke, multiple sclerosis, Parkinson's disease, or Spina bifida (diabetes mellitus is not an exclusion criterion unless it is causing diabetic neuropathy)
- undergoing active treatment, or on active surveillance, for prostate or bladder cancer (including low grade/stage transitional cell cancer[TCC])
- have previously had prostate surgery
- are not medically fit for surgery, or are unable to complete outcome assessments
- do not consent to be randomised and/or are not willing or able to comply with essential study procedures.

Sponsor

North Bristol NHS Trust Research & Innovation (NBT, R&I [ref 3250])

Funding

National Institute for Health & Research, Health Technology Assessment (HTA) Programme: Reference Number 12/140/01

ISRCTN

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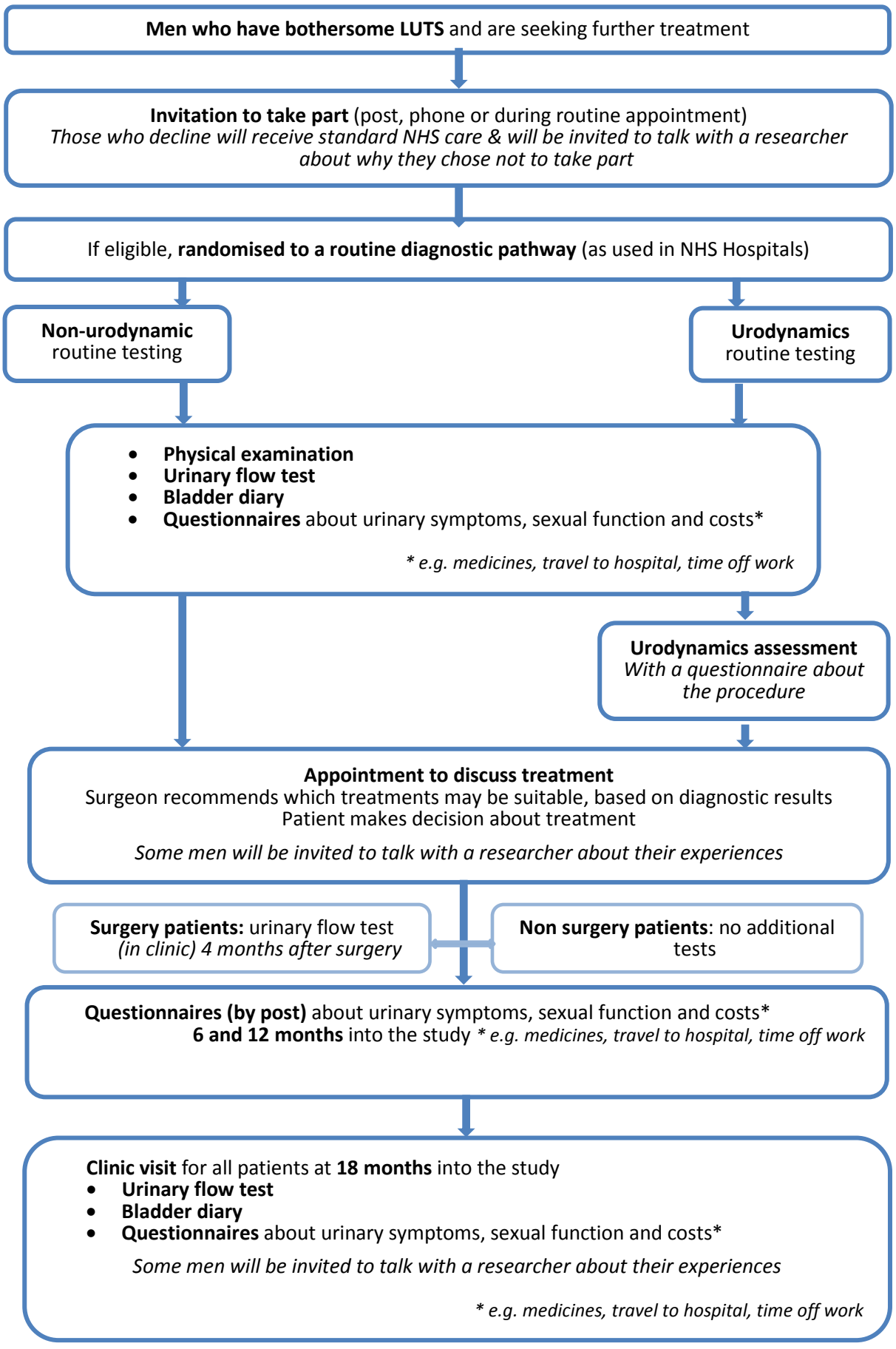
Duration

Start date: 1 April 2014
Planned finish date: 30 September 2018


Men who have bothersome LUTS and are seeking further treatment
Invitation to take part (post, phone or during routine appointment)
Those who decline will receive standard NHS care & will be invited to talk with a researcher about why they chose not to take part
If eligible, **randomised to a routine diagnostic pathway** (as used in NHS Hospitals)
Non-urodynamic routine testing
Urodynamics routine testing
• **Physical examination**
• **Urinary flow test**
• **Bladder diary**
• **Questionnaires** about urinary symptoms, sexual function and costs*
** e.g. medicines, travel to hospital, time off work*
Urodynamics assessment
With a questionnaire about the procedure
Appointment to discuss treatment
Surgeon recommends which treatments may be suitable, based on diagnostic results
Patient makes decision about treatment
Some men will be invited to talk with a researcher about their experiences
Surgery patients: urinary flow test *(in clinic) 4 months after surgery*
Non surgery patients: no additional tests
Questionnaires (by post) about urinary symptoms, sexual function and costs*
6 and 12 months into the study ** e.g. medicines, travel to hospital, time off work*
Clinic visit for all patients at **18 months** into the study
• **Urinary flow test**
• **Bladder diary**
• **Questionnaires** about urinary symptoms, sexual function and costs*
Some men will be invited to talk with a researcher about their experiences
** e.g. medicines, travel to hospital, time off work*

1. Introduction

Title of trial:

Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) for diagnosis and management of bladder outlet obstruction in men

This protocol describes a major multicentre UK trial to establish whether a care pathway not including invasive urodynamics is no worse than one in which it is included in men who are considering further treatment where surgery might be an option for bladder outlet obstruction (BOO). The study is designed to be as informative as possible, whilst remaining simple and pragmatic, both for those participating and for those involved in clinical care.

Research nurses and urologists in each centre will identify and recruit men who are seeking further treatment, which might include surgery, for BOO and collect descriptive information, symptom assessment, flow rates and urinalysis. Those who are eligible will be invited to enter a randomised trial of treatment based on that routine information only (the "Non-urodynamic assessment" control group) or routine information supplemented by urodynamic testing. All men will be followed up at 6, 12 and 18 months after randomisation.

1.1 Background

Lower urinary tract symptoms (LUTS) comprise storage symptoms (e.g. increased daytime urinary frequency, nocturia, urgency, incontinence), voiding symptoms (e.g. slow stream, intermittency, hesitancy, straining, dribbling) and post voiding symptoms (e.g. post-micturition dribble). Ninety percent of men aged 50 to 80 years suffer from at least one LUTS, which can affect quality of life, occupation and other activities. Prevalence and severity increase with age (Jacobsen *et al.*, 1996) and the progressive increase in the aged population group has emphasised the importance to our society of appropriate and effective management of male LUTS.

Identification of causal mechanisms is needed to optimise treatment. In men with LUTS, benign prostate enlargement (BPE) with ageing causes partial BOO, a situation known as benign prostatic obstruction (BPO). BPO is a major contributor to LUTS. For such patients, prostate surgery, such as transurethral resection of the prostate (TURP), has a good chance of improving LUTS. However, LUTS can also be caused by bladder dysfunction, e.g. poor expulsion strength of the bladder muscle. This is called "underactive bladder, or "detrusor underactivity", as the main bladder muscle anatomically is called the detrusor. In such men, it is hard to justify prostate surgery if BPO is not present, especially in view of potential adverse effects associated with surgery, such as blood transfusion, anaesthetic problems or incontinence.

Tests of lower urinary tract function are used in clinical practice to demonstrate the causes of voiding or storage problems. Uroflowmetry is the simplest non-invasive test of voiding function. It entails voiding into a recording device that measures the volume of urine passed and the rate of urine flow, with an ultrasound scan after voiding to see how efficiently the bladder has emptied. In addition, the NICE guidance on management of LUTS in men (CG97) (Jones *et al.*, 2010), states that invasive urodynamics may be used when invasive treatment is being considered, or for equivocal or more complex cases. Invasive urodynamics, which is also called multichannel cystometry, employs bladder catheterisation for both bladder filling and bladder pressure measurement, and rectal catheterisation for measurement of abdominal pressure. Concurrent subtraction of abdominal from bladder pressure by a computer calculates "detrusor pressure", to demonstrate whether bladder contraction is occurring. Thus invasive urodynamics can evaluate storage function (while the bladder is being filled) and voiding function (when the man passes urine). Observing high detrusor pressure associated with only a low urine flow rate is diagnostic of BOO (Abrams *et al.*, 1979). Low detrusor pressure with low flow implies that bladder contractility is impaired (Abrams, 1999). Without invasive urodynamics, it is uncertain for any given individual whether the bladder outlet is obstructed, and whether the bladder is overactive during storage or underactive during voiding.

Other diagnostic methods have been evaluated and reported with up to level 3 evidence. These include: penile cuff test (Griffiths *et al.*, 2005; Harding *et al.*, 2004); urethral reflectography (Aagaard *et al.*, 2012); ultrasound measurement of bladder wall thickness and weight (Huang *et al.*, 2012); intravesical prostatic protrusion (Park *et al.*, 2012); resistive index (Shinbo *et al.*, 2011); and prostatic urethral angle (Ku *et al.*, 2010). However, there is insufficient evidence to warrant any of these tests becoming standard practice in the clinical evaluation of male LUTS (Parsons *et al.*, 2009).

1.1.1 Health Technology Assessment (HTA) Programme

Despite the implicit merit of confirming that BOO is present before proceeding to surgery to relieve BOO, the lack of relevant research evidence means that many centres omit the test from the usual care diagnostic pathway. Invasive testing is perceived as unpleasant, and service delivery has cost implications. NICE CG97 indicates that performing an invasive procedure is a balance of the possible benefits versus the possible risks, and that these must be explained to the patient during informed consent for the procedure, and appropriate advice given should adverse events occur.

The HTA addressed this with a commissioning brief asking the research question "In men considering surgery for bothersome lower urinary tract symptoms, is diagnostic categorisation using results of invasive multichannel urodynamics worthwhile from the perspective of the men concerned and the NHS compared to not using multichannel urodynamics?"

This research was commissioned by the NIHR-HTA following prioritisation of research questions posed by the NICE Guideline Development Group, which indicated that research into the role of invasive urodynamics would clarify whether it could improve the outcome of surgery, and whether it should be recommended or not in the future (NICE, 2010). They considered that improving the chance of an accurate diagnosis and identifying potential complications was the most important outcome when considering surgical treatment.

1.1.2 Population

44,000 new cases of symptomatic benign prostatic obstruction (BPO) are diagnosed each year. Since BPO is a disease of older men (Lepor, 2004), the number of patients affected is likely to increase by almost 50% by the year 2025, in line with population ageing.

Men usually present with voiding LUTS, such as difficulty initiating the urinary stream (hesitancy), and weak urinary stream. Disease-specific HRQOL measures are significantly worse in men with higher symptom severity ratings in population-based studies (Girman *et al.*, 1998). Severe LUTS may require surgical treatment, and 25,000 surgical procedures to relieve BPO are currently performed each year in the NHS. The most widely-used approach is transurethral resection of the prostate (TURP) using monopolar or bipolar electrodes, or less commonly laser ablation (Mamoulakis *et al.*, 2009).

1.2 Rationale for current study

The NICE clinical guideline group on male LUTS (Jones *et al.*, 2010) was unable to identify any methodologically high quality clinical or economic studies. The literature has been reviewed by Parsons and colleagues (Parsons *et al.*, 2009) and by various professional groups in the last decade: the 6th International Consultation on New Developments in Prostate Cancer & Prostate Diseases (Abrams, 2006), the American Urological Association on guidelines for management of BPH (McVary *et al.*, 2011), the European Association of Urology (EAU) Guidelines on Male LUTS (Oelke *et al.*, 2012), and most recently for the 4th ICUD-SIU International Consultation on Male LUTS (Chapple *et al.*, 2013). None of these reviews was able to identify high level evidence on the use of invasive urodynamic testing in male LUTS.

We reviewed evidence for the diagnostic role of invasive urodynamics in men with LUTS prior to surgery for BPO. We identified no published RCTs with data comparing the standard practice investigation (Oelke *et al.*, 2012) (urine flow rate measurement (Qmax) and ultrasound estimate of post void residual urine (PVR)), with invasive urodynamics. One abstract did not have any useable data (Kristjansson, 1999).

Level 3 evidence exists to suggest that patient selection after invasive urodynamics maximises the outcome benefits to patients from surgery to relieve BPO, over and above that given by the standard investigations of Qmax and PVR. The AUA Guidelines recommend that the greater diagnostic benefits of invasive urodynamics over Qmax/ PVR are discussed with patients prior to the decision for prostate surgery (McVary *et al.*, 2011).

From NHS reference costs data 98,986 urodynamic studies were undertaken on men and women by 131 NHS Trusts in England in 2011-2012 at a tariff cost of £16.7 million; no information for use of invasive urodynamics specifically in men is available.

For 100 procedures, the specific equipment and consumables cost of TURP is approximately £29,000. TURP has a median hospital stay of 2 days. Significant risks may be associated: reported mortality is up to 0.25% (Rassweiler *et al.*, 2006), and morbidities can include blood loss, erectile dysfunction or incontinence, resulting in considerable distress to patients. Late complications (urethral stricture and bladder neck contracture) are reported in up to 9.8% (Rassweiler *et al.*, 2006). Additional NHS costs result from delayed discharge from hospital, re-admissions and increased primary care utilisation. These unwanted consequences will increase in the future, as surgery for BPO increases in line with the ageing male population, and because most operations are conducted on older men (in 2010-11, 41% of TURP operations were for men of 75 years or more in age). Thus, reduction in the number of surgical procedures offers direct cost savings, reduced resource use, and supports the possibility of reconfigurations of surgical services.

The British Association of Urological Surgeons (BAUS) Sections of Female, Neurological and Urodynamic Urology, and Academic Urology were involved in trial planning and have given the study their full support.

1.2.1 Health need

As men get older their prostates get bigger, often resulting in bothersome LUTS due to BPO. Additional problems that can arise with progression of BPO include: acute urinary retention (painful inability to pass urine due to complete BOO, requiring emergency catheterisation); urinary tract infections; bladder stones; and renal failure. If medical therapy fails to improve LUTS, men often request surgery to reduce their LUTS.

NHS Health Episode Statistics show that approximately 25,000 TURPs are done annually, resulting in considerable use of health resources, and the possibility of increased demand is raised by the demographics of the ageing population in the UK. Approaches to reducing the demand on health resources are needed.

1.2.2 Expressed need

The clinical benefit of invasive urodynamics is in ensuring that surgery to relieve outlet obstruction is used only in men who actually have BPO. Thus, the NICE clinical guideline on Male LUTS (Jones *et al.*, 2010) recommended the following research question: What is the clinical and cost effectiveness of multichannel cystometry (invasive urodynamics) in improving patient-related outcomes in men considering bladder outlet surgery? They stated that this research would clarify whether invasive urodynamics could improve the outcome of surgery, by identifying which patients have BPO. In addition, level 4 evidence indicates that men are unlikely to proceed to TURP if they are shown not to have BPO. Thus invasive urodynamics has the potential to reduce overall numbers of surgical interventions for BPO in the NHS.

We surveyed UK surgeons in 22 urology departments, and confirmed that this trial is a priority issue for clinical service delivery, and that there is sufficient uncertainty amongst both the surgeons and their patients regarding the two care pathways (with or without invasive urodynamics).

1.2.3 Sustained interest and intent

The general population has an increased life-expectancy, and as men get older, their prostates enlarge and cause BPO which often requires surgery. In addition, voiding symptoms become increasingly prevalent, some of which may not be due to BPO. Therefore, as the population ages, more operations will be considered to relieve BPO, some of which may not actually be appropriate. There is therefore sustained interest in the diagnostic pathway.

1.2.4 Capacity to generate new knowledge

NHS centres vary in the precise approach to diagnostic testing for men with LUTS. In some centres, Prostate specific antigen (PSA) testing is used to screen for prostate cancer or estimate prostate size. In some centres, Penile Cuff testing is used to measure bladder outlet obstruction pressures. Variations in practice may enable identification of additional studies.

The patient reported outcome measure, the ICIQ-Underactive Bladder (UAB), may be used to evaluate symptom severity and quality of life impact from the patients' perspective. This questionnaire is currently in development in accordance with the ICIQ protocol and FDA guidance for PRO development (2009). This tool will provide a valid and reliable measure of this symptom complex.

2. Study aims and objectives

In men with bothersome LUTS, we hypothesise that diagnostic categorisation of bladder outlet obstruction using invasive urodynamics improves patient selection for obstruction-relieving prostate surgery compared to a pathway with no invasive urodynamic testing. Consequently, this will make it less likely that the subgroup of men with LUTS who do not have bladder outlet obstruction will elect to undergo surgery, thereby reducing risk of harm from surgery and potentially worse symptom outcomes.

The aim of the UPSTREAM trial is to determine whether a care pathway not including invasive urodynamics is no worse for men in terms of symptom outcome than one in which it is included, at 18 months after randomisation. This primary clinical outcome will be measured with the widely-used patient reported outcome, the International Prostate Symptom Score (IPSS) at 18 months post-randomisation. We will also establish whether inclusion of invasive urodynamics reduces rates of bladder outlet surgery as a main secondary outcome.

The objectives are to answer the following questions:

- Does invasive urodynamics deliver similar or better symptomatic outcomes for LUTS measured by the International Prostate Symptom Score (IPSS) at 18 months after randomisation?
- Does invasive urodynamics influence surgical decision making, as reflected in differing surgery rates in the two diagnostic pathways?
- What is the cost effectiveness of the two diagnostic pathways, by calculating the incremental cost per quality-adjusted life-year gained (QALYs) at 18 months post randomisation?
- What are the relative harms of invasive urodynamic tests, and surgical and conservative management?
- What subsequent NHS services are required (including repeat surgery or catheterisation for acute urinary retention) for men in each arm?
- What are the differential effects on other outcomes, such as quality of life and general health?

A qualitative component has been embedded within the trial to establish patient-perceived importance of different outcomes, explore patients' and surgeons' perspectives on experiences of procedures and acceptable inferiority margins, and determine reasons for failure resulting in crossover to alternative surgery. This qualitative work will also answer the following questions:

- What is the acceptability of invasive urodynamic tests for men, and how satisfied are men with the diagnostic pathways for LUTS being tested?
- How does invasive urodynamic testing impact on decision making for both surgeons and men with bothersome LUTS, assessed using qualitative methods?

3. Study design

A two-arm trial randomising men with bothersome lower urinary tract symptoms (LUTS), for whom surgeons would consider offering surgery, between a care pathway based on urodynamic tests with invasive multichannel cystometry ("Urodynamics" active intervention arm) and a care pathway based on non-invasive routine tests, i.e. without multichannel cystometry ("Non-urodynamic assessment" control arm).

Diagnostic pathways and thresholds of testing were informed by a preliminary survey of 30 UK surgeons in 22 departments, which we undertook in 2012. This showed that the minimum baseline dataset comprises International Prostate Symptom Score (IPSS), maximum urinary flow rate (Qmax) with post-void bladder ultrasound scan and urinalysis. Some centres also use "discretionary tests" (e.g. PSA blood test or penile cuff testing).

3.1 Setting

Urology departments of at least 26 NHS Hospitals in the UK. These currently include: Southmead Hospital, Bristol; Freeman Hospital, Newcastle upon Tyne; Royal Devon and Exeter Hospital, Exeter; Musgrove Park Hospital, Taunton; Southport and Formby District General Hospital, Southport; Kingston Hospital, Kingston upon Thames; Royal Hallamshire Hospital, Sheffield; Epsom General Hospital, Epsom; Queen Elizabeth Hospital, Birmingham; Kent and Canterbury Hospital, East Kent and Canterbury; Salisbury District General Hospital, Salisbury; Lister Hospital, Stevenage; Churchill Hospital, Oxford; The James Cook University Hospital, Middlesbrough; The Queen Elizabeth Hospital, King's Lynn; Royal Free Hospital, London; Royal Liverpool University, and Broadgreen, Hospitals; Torbay Hospital, Torbay; Southampton General Hospital, Southampton; Kettering General Hospital, Kettering; Charing Cross Hospital, London; Royal Berkshire Hospital, Reading; Derriford Hospital, Plymouth; West Cumberland Hospital, Cumbria; Sunderland Royal Hospitals, Sunderland; and St George's Hospital, London.

Additional sites will be identified if required.

3.2 Participants

Men with bothersome LUTS and suspected bladder outlet obstruction (BOO) for whom surgeons would potentially offer surgery.

3.3 Inclusion criteria

Men seeking further treatment for their bothersome LUTS which may include surgery.

3.4 Exclusion criteria

- Unable to pass urine without a catheter (urinary retention) (excluding CISC after void to empty)
- Relevant neurological disease, such as a stroke, multiple sclerosis, Parkinson's disease, or Spina bifida (diabetes mellitus is not an exclusion criterion unless it is causing diabetic neuropathy)
- Undergoing active treatment, or on active surveillance, for prostate or bladder cancer (including AS for low grade/stage transitional cell cancer [TCC])
- Previous prostate surgery
- Not medically fit for surgery, or unable to complete outcome assessments
- Men who do not consent to be randomised and/or are not willing or able to comply with essential study procedures.

3.5 Planned Interventions

3.5.1 Baseline clinical assessment for all men

Following consent and randomisation, all men will undergo assessment as set out in the NICE clinical guideline on Male LUTS (NICE, 2010);

- Assessment of general medical history to identify possible causes of LUTS, and associated comorbidities. Review of current medication.
- Physical examination guided by urological symptoms and other medical conditions, an examination of the abdomen and external genitalia, and a digital rectal examination (DRE).
- Urinalysis (dipstick, or microscopy and culture)
- Urinary frequency volume chart (bladder diary).
- Measurement of urinary flow rate, with post void residual volume measurement by ultrasound. *(Note: a urinary flow rate test recorded up to 6 months prior to date of informed consent is acceptable, to avoid unnecessary repeat for the patient)*

3.5.2 Discretionary tests

As this is a pragmatic trial, additional tests may be undertaken according to the usual practice of the research sites. For example, the following tests may be undertaken in line with the NICE clinical guideline on Male LUTS (NICE, 2010);

- Information, advice and time to decide if they wish to have prostate specific antigen (PSA) testing if their LUTS are suggestive of BPO, or their prostate feels abnormal on DRE, or they are concerned about prostate cancer.
- Cystoscopy only when clinically indicated, for example: recurrent infection, sterile pyuria, haematuria, profound symptoms, or pain.
- Imaging of the upper urinary tract when clinically indicated, for example: chronic retention, haematuria, recurrent infection, sterile pyuria, or pain.

3.5.3 Interventions for randomised men

"Non-urodynamic assessment" Control arm (Usual care).

Men will have clinical treatment based on the baseline clinical assessment described above (section 3.5.1).

Intervention arm (Usual care plus urodynamics assessment).

Men will undergo the routine baseline clinical assessments set out above (section 3.5.1). In addition, they will undergo invasive urodynamics, in which catheters are used to measure bladder and abdominal pressures, during bladder filling and passing urine. Invasive urodynamics is used to calculate voiding parameters (bladder outlet obstruction index, contractility) and assess urine storage (detrusor overactivity, bladder capacity). Hence, it should distinguish men with bladder outlet obstruction, who should benefit from surgery to relieve obstruction, from men with reduced bladder contractility, who are unlikely to benefit from surgery, or those without obstruction with storage disorders or normal urodynamic findings.

3.6 Method of urodynamic testing

Quality of urodynamic testing will be according to International Continence Society Good Urodynamic Practice requirements (Schafer *et al.*, 2002). The following technical aspects of invasive urodynamic testing will be reviewed for each centre (mandatory):

- Appropriate equipment maintenance and calibration testing consistent with manufacturer instructions according to the unit log
- Measurement of bladder and abdominal pressure, including resting pressures within expected limits
- Concurrent computing of detrusor pressure
- Extrinsic filling at "physiological rates"
- Checks of pressure transmission (e.g. subtraction of cough impulse) during filling and after voiding
- Trace labeling for later re-interpretation; e.g. reporting of key events (e.g. detrusor overactivity, permission to void), bladder sensations and timing of "provocation tests" and "permission to void"

- Correction for artefacts during computation of BOO and bladder contractility indices
- Correspondence of written report to symptoms and specific features of the original traces

3.7 Surgical management

After diagnostic testing with (intervention arm) or without ("Non-urodynamic assessment" control arm) urodynamics, patients will see their surgeon to decide on whether to proceed to surgical treatment. The treatment decision is between the urologist and the patient and there are no treatment 'requirements' imposed by the UPSTREAM study. We aim to capture urologist and patient opinions about treatment decisions in the relevant case report form(s). As a pragmatic trial, standard practice for the centres will be followed, relating to type of surgery (providing it is a NICE approved surgical procedure, e.g. monopolar or bipolar TURP, or laser), whether to stay on LUTS medications, antibiotic prophylaxis and other factors. Type of surgery will be recorded. All conservative and surgical management plans and actual treatment received will be documented. As this is a pragmatic study, surgeons may feel it necessary in some cases to conduct additional tests outside of the participants allocated intervention group. Centres are asked to record, in the baseline case report form (CRF), whether the participant received the diagnostic assessments that they were randomly allocated too, and provide reason(s) if assessment was different to that allocated. As we are recording assessments received versus assessment allocation in trial document, such a deviation would not require additional 'Protocol Noncompliance' reporting.

All other GCP and/or Protocol deviations should be recorded on the 'GCP/Protocol Noncompliance Report Form' (provided in the Site File) and forwarded to the Trial Manager (amanda.lewis@bristol.ac.uk or helen.winton@bristol.ac.uk), who will notify the Chief Investigator and Trial Sponsor.

3.8 Allocation to trial groups

All eligible and willing men will be randomly allocated to receive one of two assessment pathways, as outlined above in Section 3.5; that is either a) usual care (non-urodynamics, control); or b) usual care plus urodynamics assessment (intervention).

All men who enter the study will be logged with the central trial office and given a unique 6-digit Study (Participant) Identification Number. Randomisation will utilise the existing proven remote automated computer randomisation application at the study administrative centre in the Bristol Randomised Trial Centre (BRTC, a fully registered UK CRN clinical trials unit) in the University of Bristol. The randomisation application will be available to participating centres, both as a telephone based IVR system and as an internet based service, for them to complete the randomisation procedure themselves, on site.

Further details of 'Identification, Recruitment and Consent' are outlined in Section 4.1, below.

3.9 Study outcome measures

The measures have been selected according to the specifications of the HTA commissioning brief.

3.9.1 Primary outcome measure

- Primary clinical outcome: difference in lower urinary tract symptom (LUTS) between the two arms at 18 months (post randomisation), measured with the International Prostate Symptom Score (IPSS). IPSS is validated (Barry *et al.*, 1992), well-known and widely used in the NHS.

3.9.2 Secondary outcome measures

- Surgery rate (the relative proportion of men in each group having surgery up to 18 months after randomisation).
- Cost-effectiveness analyses from the perspectives of the NHS, Personal social services and patients. Subsequent need for surgery (related to their LUTS) during any stage of the trial will be recorded.
- Adverse events of testing and treatment (e.g. infection, acute urinary retention).

- Measures from the International Consultation on Incontinence Questionnaires (ICIQ) (Abrams *et al.*, 2006) will be used alongside the IPSS, giving sensitive and comprehensive assessment of LUTS severity/ bother, sexual function, quality of life and satisfaction with urodynamic testing. The following will be measured at 6, 12 and 18 months;
    - IPSS
    - ICIQ Male LUTS (ICIQ-MLUTS)
    - ICIQ sexual function in Male LUTS (ICIQ-MLUTS-sex)
    - ICIQ urodynamics satisfaction (ICIQ-UDS-S) will be administered at a single time point after urodynamic testing for the interventional arm.
- Maximum urinary flow rate (Qmax) at 18 months. In men undergoing surgery in both arms, an additional Qmax measure at 4 months after operation will be used as a quality measure for surgery.
- The EQ-5D-5L will be used to provide the quality of life weights used to calculate Quality adjusted life years (QALYs).
- Qualitative interviewing will explore user acceptability and influences on decisions made by the participating men and the surgeons.

In addition, all men will be invited to consent to long term follow up, including use of computerised NHS records, HES data and other routine data sources.

4. Participant entry

4.1 Identification, recruitment and consent

All eligible men referred with voiding LUTS will be identified by the consultant, dedicated research nurse, or designated team member at time of receipt of referral letter or during patients' clinical appointments. Hospital staff should complete trial-specific screening logs for all potentially eligible men and provide confirmation of the patient's outcome for the study; this will be one of three: 1) patient confirmed as ineligible; 2) patient was eligible but declined to take part; and 3) patient was eligible and consented to take part. These will be reviewed by the UPSTREAM Office team (BRTC) on a monthly basis.

Due to variation in patient pathways in each hospital, these arrangements should be individualised according to local circumstances in each site. Those patients identified from referral letters will be sent a Patient Information Sheet (PIS), Assessment Information Sheet (AIS) and covering letter. Alternatively, the research nurse will describe the study to the patients at their clinical appointment and, if interest is expressed, provide further details of the study by means of the PIS and AIS.

An approved study specific poster can also be displayed in suitable clinic rooms, which provides the contact details of trial related staff that interested men can contact for further information.

If the patient agrees to the study, they will be given a chance to ask questions and should ideally have at least 24-hours to think about taking part before being consented and randomised. Written informed consent will be obtained from all patients who agree to take part in the study. The PIS and the consent form will refer to the possibility of long-term follow-up and being contacted about other research if the man is willing. If, however, the patient is happy to take part in the study without having been given PIS and study details over at least 24 hours ago, and requests to provide written consent and complete baseline questionnaires at that time (i.e. to avoid having to return to the hospital for an additional appointment) this is possible. In such cases we suggest that the research centre completes written consent and baseline questionnaires, there and then, but does not randomise the patient until at least 24 hours have passed. After at least 24 hours, the centre should contact the patient by telephone to confirm they are still willing to proceed with the study, and if so, the centre can proceed with randomisation and inform the patient of his intervention

allocation, via the telephone. If the patient has changed his mind, however, and no longer wishes to be randomised, the research centre should complete the 'UPSTREAM Change of Permissions / Withdrawal Form' accordingly, and follow essential reporting procedures specified on the form. For clarity, a copy of the consent form and completed Change of Permissions/Withdrawal Form should be kept at site, as well as forwarded to the UPSTREAM Office Team for records. All other data collected for such a patient, however, such as baseline questionnaires, should be suitably discarded by the research site; the trial has no need to retain this information as the patient decided not to enrol (be randomised) into the trial. For men who are randomised, the research centre should also record that the patient opted for this consent and randomisation approach in their medical notes, and in the UPSTREAM Baseline CRF (Comments section). This alternative consent and randomisation process helps the patient to avoid returning the hospital simply for the purpose of the trial.

Men who are not willing to be randomised, but who would otherwise be eligible, will be asked to consent to being contacted for qualitative research to explore reasons for non-participation.

All men who enter the study will be logged with the central trial office and given a unique 6-digit study (participant) identification number, and randomised (as outlined in Section 3.8). Hospital staff will complete and send a study approved letter to the participant's General Practitioner (GP) informing them that their patient has 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 Withdrawal criteria

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.

4.2.1 Withdrawal reporting procedures

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).

4.3 Feasibility phase

Important notice: the Trial Steering Committee (TSC) met in January 2015 and approved a revised timescale and revised group of centres for an extended feasibility phase, with additional reporting to the TSC upon conclusion (expected May 2015). Please refer to Section 9.4 for details.

Original feasibility phase: The feasibility phase is intended to verify that recruitment is possible. It will use data from four selected pilot centres (Bristol, Kingston-upon-Thames, Newcastle and Taunton). The pilot sites will be launched sequentially in months four and five from project initiation. The feasibility phase will conclude when 12 site recruitment months have been completed (end of month nine, i.e. December 2014). The timing of assessment will enable confirmation of feasibility at an early stage in the trial.

Proportionately, 12 site recruitment months should yield 48 subjects out of the overall accrual target of 800. The "go" criteria will be applied, as follows:

- At least 75% (36/48) of accrual target, or
- At least 50% (16/32) of target in the first two months and 75% (12/16) or better in the third evaluation month of the feasibility phase.

The criteria allow for the fact that sites usually take a few weeks to achieve steady state and recruit efficiently.

If neither of the "go" criteria is achieved, but there are good indications that recruitment is increasing, or that logistical issues hindering recruitment can be resolved (by for example replacing non-recruiting sites), then an action plan will be devised by the trial management group (TMG) to address the issues. The TSC will review the action plan at a formal meeting and advise the HTA Board on the likelihood of recruitment success, and whether a further feasibility assessment is warranted.

In addition, up to 10 centres will be set up during the feasibility phase to maintain the necessary rate of recruitment over the subsequent trial recruitment period and in anticipation of continuing to the full trial.

5. Randomisation, blinding and prevention of bias

5.1 Randomisation

All men who enter the trial will be logged with the central study office and given a unique, 6-digit Study (participant) Identification Number. Randomisation will utilise the existing proven remote automated computer randomisation application at the study administrative centre in the BRTC. Participants will be randomly allocated to treatment arms using an automated web/telephone randomisation system provided by the BRTC. Randomisation will be stratified by centre.

5.2 Blinding

Blinding in the urodynamic unit is not possible nor appropriate in this pragmatic trial, given that men are only catheterised in the invasive group, hence group allocation cannot be concealed from the man or the staff. We do not feel it is necessary or ethical to perform sham catheterisation to conceal the nature of testing. Furthermore knowledge of the results of urodynamic testing underpins the urologist's ability to make a management decision, in conjunction with his patient, so neither the man nor his urologist can be blinded to the intervention or its findings. However, outcome assessment is largely by participant self-completed questionnaire, so avoiding interviewer bias. Additional methods to protect against bias are discussed in section 5.3, below.

5.3 Methods to protect against bias

5.3.1 Urodynamic techniques:

The urodynamic assessment will be undertaken according to International Continence Society (ICS) Good Urodynamic Practices guidance (Schafer *et al.*, 2002), and compliance of the procedures in the urodynamic units with this internationally-recognised standard will be confirmed by the clinical grant applicants. We will centrally monitor deviations from agreed protocols and review >10% traces from each research centre. All investigators are already experienced urodynamics investigators, or work with an experienced urodynamics unit meeting the national minimum standards (http://www.ukcs.uk.net/docs/joint_statement.pdf).

5.3.2 Standardisation of surgical techniques:

All investigators are already experienced prostate (TURP) surgeons. The research nurses and the surgeons will complete a Peri-Operative CRF (developed for our other trials and adapted for UPSTREAM) at the time of surgery, including any intra-operative difficulties or complications. As this is a pragmatic trial, surgical procedure and postoperative care will be according to local centre practice.

5.3.3 Loss to follow up (attrition bias)

Loss to follow-up in our previous trial of conservative treatment for men with urinary incontinence after prostate surgery (Glazener *et al.*, 2011) was 5 to 10% at one year. However, a more conservative estimate of just over 20% loss to follow up has been used in the sample size calculations. We will take very active measures to minimise loss of men from the study in line with Research Ethics Committee approval, such as reminder letters, phoning/ texting/ emailing the men, obtaining back-up 'best contact' addresses, using non-contingent retention incentives (Edwards *et al.*, 2009), and

checks with their GPs (Robinson *et al.*, 2007). In addition we will obtain consent from the men to enable us to access centrally-held NHS data, for example via the NHS Strategic Tracing Service in England and Wales to find new addresses, and electronic data linkage which records any in-patient episodes and outpatient visits. We have extensive experience of using such strategies and measures, and have received Ethics approval to do so in previous studies.

5.3.4 Other sources of bias (detection bias)

It will not be possible to blind participants or caregivers of their study arm allocation. Their GP will be informed and participants will be made aware of this.

Where feasible, research staff will be blinded to allocation while conducting data collection for outcomes, performing data entry and analysis, and by using Study Numbers only to identify men, questionnaires and diaries. Men will be asked not to reveal information about their diagnostic evaluation and treatment. Staff will be asked to record whether or not they knew to which group the man had been allocated and hence which diagnostic tests were performed before undertaking outcome assessments. All men will be actively followed up, with analysis based on the intention-to-treat principle. All analyses will be clearly predefined to avoid bias.

6. Adverse events

6.1 Definitions

6.1.1 Adverse event (AE)

An adverse event (AE) includes any untoward medical occurrence in a study participant, including abnormal laboratory results, symptoms or a disease that does not necessarily have a causal relationship with procedures required by the protocol. 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 <u>not</u>:

- continuous and persistent disease or symptom, present before the trial, which fails to progress;
- signs or symptoms of the disease being studied; or
- treatment failure.

For the UPSTREAM study, pre-planned hospitalisation or elective procedures, e.g. for pre-existing conditions which have not worsened, does not constitute an AE. 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 AE.

6.1.2 Serious adverse event (SAE)

An adverse event is defined as "serious" (SAE) if it:

- 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 inpatient hospitalisation
- Results in persistent/significant disability/incapacity
- Is otherwise considered medically significant by the investigator *

* 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, may also be considered serious. Medical judgment will be exercised in deciding whether an AE is serious in other situations.

6.1.3 Expected, related adverse events

Within UPSTREAM, 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 and whether or not it would have been administered outside the study as normal care.

The following events are expected, related adverse events during/after any diagnostic procedures:

- urinary tract infection
- bacteriuria
- haematuria
- urinary retention
- discomfort
- dysuria
- urethral trauma

The list below itemises the expected, related adverse events summarised from the literature for prostate surgery:

- excess blood loss (>500 ml);
- blood transfusion;
- urethral injury;
- bladder injury;
- bowel injury;
- injury to blood vessels or nerves
- anaesthetic complications;
- thrombosis/DVT/pulmonary embolism;
- prolongation of post-operative catheterisation;
- recatherisation;
- urinary tract infection;
- other infection (sepsis, septicaemia, abscess);
- new urinary tract symptoms;
- constipation;
- discomfort / pain;
- new sexual problems;
- death

Complication rates will be recorded and classified using the internationally accepted Clavien-Dindo classification in trial CRFs (Dindo *et al.*, 2004).

6.2 Reporting procedures for adverse events

Within UPSTREAM, **all** adverse events should be recorded on the 'UPSTREAM Adverse/Serious Adverse Events' 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) should also be recorded on the 'UPSTREAM Adverse/Serious Events' form.

All adverse events should be reported to the UPSTREAM Study Office Team; 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 Trial Manager / Chief Investigator in the first instance. Specific details of adverse / serious adverse event reporting

can also be found in the relevant study specific standard operating procedure, which should be kept in the UPSTREAM Site File.

6.2.1 Non serious adverse events

All adverse events (AEs), whether expected or not, should be recorded using the 'UPSTREAM Adverse/Serious Adverse Events' form. A copy of the completed form should be forwarded to the UPSTREAM study office team within a timely manner (i.e. within <4-weeks of becoming aware), and also kept in both the Site File and patient's notes. The UPSTREAM online database *(once available)* will be updated accordingly by the UPSTREAM Office Team at the earliest opportunity.

6.2.2 Serious Adverse Events (SAEs):

Local PI or Research Nurse: ***All SAEs*** including deaths from any cause (related or otherwise) should be recorded on the 'UPSTREAM Adverse/Serious Adverse Events' form, whether originally notified on a CRF, participant questionnaires or by other means. The 'UPSTREAM Adverse/Serious Adverse Events' form should be:

a. Signed by the Local PI
b. Scanned and emailed (preferably) or faxed to the Trial Manager **within 24 hours** of learning of a SAE, or **within 24 hours** in the event of a death

- Scan and email SAE forms to: Amanda Lewis (amanda.lewis@bristol.ac.uk) or Helen Winton (helen.winton@bristol.ac.uk), cc Marcus Drake (marcus.drake@nbt.nhs.uk). Telephone: Amanda/Helen on 0117 331 3907 or Marcus on 07764 662017. *(Please note typical working hours: Monday to Friday, 09:00-17:00)*

- Fax SAE forms (marked URGENT) to: Dr Amanda Lewis or Dr Helen Winton on 0117 928 7325
If using fax: Sites **MUST** notify us (by telephone/email) in advance as the fax machine is unmonitored. We will acknowledge receipt by email but sites cannot assume that a fax has been received until they have email confirmation of receipt.

c. This should be followed-up by sites with a phone call or email to confirm it has been received
d. The information should then be filed in the Site File and patient's records. The UPSTREAM Office Team will enter the data onto the UPSTREAM electronic database *(once available)*
e. A copy of the signed form should be kept in the Site File and in the patient's notes

NOTE: In the event that the Local PI is unavailable and the Research Nurse suspects the adverse event is Serious, the Research Nurse should complete the 'UPSTREAM Adverse/Serious Adverse Events' form as noted above, inform the Trial Manager by phone or email (if email, confirm receipt), and update the UPSTREAM electronic database *(once available)*.

Chief Investigator (CI) / or Trial Manager (TM):

1) The Trial Manager will inform the CI of all SAEs. If, in the opinion of the local PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the sponsor within 15 days (24 hours in the event of death) of receiving the AE notification. The sponsor will provide an assessment of the SAE.
2) The CI (or Trial Manager) will report any *related* and *unexpected* SAEs to the main Research Ethics Committee and the Data Monitoring Committee within 15 days of the CI becoming aware of it.
3) All related SAEs will be summarised and reported to the Ethics Committee, the Funder, the Data Monitoring Committee and the Trial Steering Committee in their regular progress reports.

7. Assessment and follow-up

7.1 Clinical outcomes

Clinical outcomes will be assessed by participant-completed questionnaires at baseline, 6 months (postal [or online or by telephone if required]), 12 months (postal [or online or by telephone if required]) and 18 months post randomisation (clinic appointment). Free flow rate testing (maximum flow rate, voided volume, post void residual) will be used at baseline and 18 months; an additional measurement of flow rate in men undergoing surgery in both groups at 4 months after surgery (+/- 1 month) will provide objective assessment of effective relief of BOO.

The research nurse will complete case report forms, both at the time of diagnostic testing and after subsequent treatment including surgery, providing details of the testing, operative procedures, complications and resource use in hospital. We are using standardised outcome instruments developed by the International Consultation on Incontinence (ICI) for urinary and sexual symptoms (Abrams *et al.*, 2006). The components and timing of follow-up measures are shown in Table 1.

7.1.1 Measurement outcomes table: components/ timing

	Baseline	Urodynamics	Peri-operative	4 mths post surgery	6 mths	12 mths	18 mths
	All pts	UDS pts	Surgery pts	Surgery pts	All	All	All
CRFs	●	●	●	●			●
IPSS	●				○	○	●
ICIQ-MLUTS	●				○	○	●
ICIQ-MLUTSsex	●				○	○	●
ICIQ-UDS-S		●					
Flow rate/ PVR	●			●			●
EQ-5D-5L	●				○	○	●
Resource use questionnaire	●				○	○	●
Bladder diary	●						●
Case note review							◊
Qualitative interview * *(selected patients)*		Patients in both arms, 1-8 weeks after treatment decision		Patients in both arms who had surgery, 6 weeks-4 months after surgery			
Qualitative interview *(staff)*							●

● Clinic/Hospital, ○ Postal, ◊ Hospital sources,* at home or by telephone

Where possible, telephone interviews will be conducted with men who withdrew or declined randomisation.

Steps will be taken to minimise loss to follow up, including reminder letters and phone calls. In particular, the primary outcome measure (IPSS at 18-months post randomisation) could be collected via the telephone if necessary.

7.2 Economic data collection

Resources used in relation to the management of bothersome lower urinary tract symptoms will be measured from randomisation to 18-months follow up. The case report forms will be used to measure: the initial hospital resource use during the diagnostic phase of the trial and the perioperative stay for those men who subsequently undergo surgery. Information Technology (IT) or similar Departments in all sites will be contacted to provide, if possible, electronic information in relation to inpatient stays, outpatient visits or any other type of hospital use that the participant has had during the 18 months of follow-up. If Hospital Patient-linked information costing systems cannot be accessed to obtain this information then a case report form will be used to record with the exception of any initial surgery, any in-patient stays, out-patient visits and procedures occurring at the treating hospitals, where the study has research governance approval, from the end of the diagnostic phase until the end of the 18 month follow-up period for any man who has had any non-routine follow-up hospital care, as identified at the 18 month clinic follow-up. The CRFs will be designed, so that the resource use collected can be costed using NHS tariffs. At baseline, 6 and 12 months follow-up the men will be given a study designed Resource Use Log (RUL) to be used as an aide memoire in which to record prospectively NHS hospital and community based health care use, medications, social service resource use time off work and any other expenses resulting from their treatment. The baseline RUL (0-6 months) will be given to the patients at the baseline assessment clinic; all subsequent RULs will be posted by the UPSTREAM Office team. These logs will reflect the design of the 6, 12 and 18 month resource use questionnaires respectively. At the baseline and 18 month follow-up clinic appointments resource use questionnaires will be interviewer administered if time permits, otherwise the questionnaires will be given to the men at the clinics for them to complete in their own time, and return them by post if necessary. At 6 and 12 month follow-up, self-completed resource use questionnaires will be posted to the men for them to complete, using the information from the RUL.

The EQ-5D-5L will be included within the questionnaires given to all men at baseline, 6, 12 and 18 months follow-up.

7.3 Qualitative data collection

7.3.1 Aims and Objectives

The aim of the study is to understand patients' and health care professionals' views and experiences of invasive urodynamic testing for male bladder outlet obstruction and bladder outlet obstruction surgery.

Objectives:

1. To explore through qualitative methods patients' views, experiences and beliefs about lower urinary tract symptoms (LUTS).
2. To examine patients' understanding and knowledge of testing for bladder outlet obstruction and treatment expectations.
3. To understand patients' and health care professionals' experiences of the trial, including their experience, opinions, acceptability and feasibility of invasive urodynamic testing/non-urodynamic assessment.
4. To investigate patients' and health care professionals' decision making regarding surgery for male bladder outlet obstruction.
5. To use qualitative methods to understand barriers and facilitators to Invasive urodynamic testing.
6. To explore the information and support needs of patients and health care professionals in relation to invasive urodynamic testing and bladder outlet obstruction surgery.
7. To investigate patients' and health care professionals' experiences, attitudes and opinions regarding male bladder outlet obstruction surgery and recovery.

7.3.2 Overview

In order to examine the views and experiences of invasive urodynamic testing for male bladder outlet obstruction we will conduct in-depth semi-structured qualitative interviews with patients and health care professionals involved in their

care. Qualitative findings will help to illuminate the perceived effectiveness and acceptability of invasive urodynamic testing for male bladder outlet obstruction and its impact on clinical decision making and explore any barriers to uptake outside of the trial.

Qualitative methods have been chosen as the most appropriate means to achieving a deep understanding of beliefs and perceptions of key medical events (Malterud, 2001; Britten, 1995). Interviews allow for the exploration of complex and sensitive issues, allowing participants to engage in a dialogue in their own language and drawing on their life experiences to explore the issues which are important to them,

Previous studies have successfully utilised qualitative methods to investigate patients' views, experiences and health beliefs about lower urinary tract symptoms (LUTS) (Glover, 2005; Gannon et al, 2004; Wareing, 2005; Welsh et al, 2011), triggers and barriers to help seeking (Shaw et al, 2001) perspectives on treatment outcomes (Coyne, et al, 2010). However, to our knowledge to date no studies have examined patients and health care professionals' views and experiences regarding invasive urodynamic testing for bladder outlet obstruction.

We are combining qualitative methods and controlled trial methods as has long been advocated (e.g. Weaver et al 1996). Qualitative methods are valuable to improve our understanding of the experiences of patients receiving, and staff delivering, an intervention (Campbell et al, 2000; Donovan et al 2002; Lewin, Glenton, and Oxman, 2009). Such use of qualitative methods in randomised controlled trials, specifically as part of pre-intervention development and post hoc interpretation, is well established (Finch, 2003; Flottorp, 2003; Sandelowski, 1996; Toroyan, 2004) and recommended (MRC, 2000).

7.3.3 Study design

In-depth interviews (Dicicco-Bloom B, Crabtree, 2006) will be conducted with trial participants (from all arms of the trial), either face-to-face or by telephone. Purposive sampling will ensure that adequate numbers of interviews will be conducted with men from each of the possible randomised groups according to treatment allocation.

Firstly, participants will be interviewed between one and eight weeks after a decision has been made regarding treatment. These interviews will consider and compare their views and experiences of the trial, explore participants' experiences of LUTS, understanding and knowledge of bladder outlet obstruction, views and experiences of invasive urodynamic testing, decision making regarding surgery and information and support needs.

A second interview will be conducted with a second group of participants from both randomised groups who had surgery following their treatment decision. Interviews will be conducted 6 weeks to 4 months after surgery to ensure that their initial recovery from surgery is complete, but recent enough that they can remember events. These interviews will explore views and experiences of treatment, decision-making and recovery.

Telephone interviews will be conducted with a sample of men who withdrew from the trial.

In addition, telephone interviews will be conducted with those that declined to be randomised in the trial.

Health care professionals will also be interviewed at the end of the trial to gather data on their views and experiences of assessment with and without urodynamics, information and support needs and their attitudes to its future implementation.

7.3.4 Participant sampling and recruitment

Purposive theoretical sampling will select participants in order to attempt to capture maximum variation in views and experiences in order that they adequately reflect those of a range of patients with LUTS considering treatment, and health care professionals involved in their care.

A sample of men in the trial will be asked if they are willing to be contacted about taking part in a qualitative interview at the time of trial consent. From participants who indicate that they are willing to be contacted, a purposive sample will

be drawn in relation to (i) geographical location of trial site. (ii) arm of the trial and (iii) total IPSS score, categorised as high (≥20) or low (≤19), (iv) socio-demographic variables such as age, ethnicity and socio-economic status (with participants being selected from areas of high and low social-economic deprivation, based on Index of Multiple Deprivation (IMD2007) score (Noble et al, 2008)). For pre-treatment interviews, we will use patients' baseline IPSS scores for purposive sampling. For post-surgery patients, we will use IPSS scores submitted at either 6, 12 or 18 months post-randomisation to sample men who have responded well/poorly to surgery (with the IPSS score also falling within the 6 week-4 month post-surgery window).

Health care professionals (e.g. urologists, urodynamics technicians, nurses, etc.) involved in the trial will be purposively sampled in relation to (i) the trial site and (ii) length of time since qualification. Those sampled will be contacted by telephone/email by the researcher and asked if they are interested in taking part in an interview. The researcher will arrange the interview at a convenient time and place and send a confirmation letter.

The sample sizes will be determined by the need to achieve data saturation, such that no new themes are emerging from the data by the end of data collection (Sandelowski, 1995). Interviews will be analysed in batches, and sampling will continue until no new themes are emerging from the interviews. This is likely to include up to thirty health care professional and forty five face-to-face or telephone trial patient interviews and twenty phone interviews with those that declined trial participation or withdrew from the trial.

7.3.5 Sampling frame

Arm	Urodynamic testing				Non invasive testing				Total
Treatment	Surgery		Conservative		Surgery		Conservative		
IPSS score	High	Low	High	Low	High	Low	High	Low	
Pre treatment (after treatment decision)	4	4	4	4	3	3	3	3	28
Post surgery	4	4			4	4			16
Total trial interviews (to inlude a mix of older/younger, randomised groups receiving surgery or conservative treatment & location (weighted towards bristol)									44
Telephone interviews with decliners and withdrawals (approximately 20 mins each)									20
Grand Total									64

7.3.6 Interview conduct

All interviews will be conducted by telephone or face-to-face, in a location of the participants' choice. Participants will be asked to provide their written, informed consent to take part immediately before the interview. A flexible topic guide will be used in order to assist questioning during in-depth individual interviews. The topic guide will be devised to ensure that the primary issues are covered across all interviews, but do not dictate data collection. The topic guide will incorporate considerable flexibility to enable participants to introduce new issues unanticipated by the researchers. Topic guides will be modified as necessary throughout the course of the study to reflect findings as they emerge. The researcher will use open-ended questioning techniques to elicit participants' own experiences and views of key events and participants will be asked to provide examples. Interviews with health care professionals are expected to last around

30 minutes and interviews with patients' are expected to last around 1 hour. With informed consent from participants, interviews will be recorded using a digital voice recorder, transcribed and anonymised to protect confidentiality.

7.3.7 Data Analysis

Interview transcripts will be checked for accuracy and then imported into NVivo qualitative data analysis software, which aids the management and indexing of qualitative data. Analysis will begin shortly after data collection starts, will be ongoing and iterative. Analysis will inform further data collection: for instance, analytic insights from data gathered in earlier interviews will help identify any changes that need to be made to the topic guide during later interviews.

Thematic analysis (e.g. Braun and Clarke, 2006), utilising a data-driven inductive approach (Boyatzis, 1998), will be used to scrutinise the data in order to identify and analyse patterns and themes of particular salience for participants and across the dataset using constant comparison techniques (Glaser and Strauss, 1967; Charmay, 2006).

Firstly, the transcripts will be read several times, to gain familiarisation with the data and initial ideas noted. The transcripts will then be examined on a line-by-line basis with Inductive codes being assigned to the segments of the data that provide insight into the participants' views and understanding of their experiences. An initial coding frame will be developed and new data will be compared initially to previous data, and then to the properties of emerging categories that contain the main themes. The process of constant comparison will allow for the generation of new themes, re-classify themes and incorporating themes within other themes (Glaser and Strauss, 1967; Charmay, 2006) and the coding frame will be modified, if needed, as analysis develops. The data will be scrutinised for negative cases and reasons for the deviance will be explored by comparison with the whole dataset.

Transcripts from the patients' and health care professionals' interviews will be analysed separately, with coding frames being developed for each separate phase of the research. A subset of transcripts will be independently double-coded by other members of the research team and compared; any discrepancies will be discussed within the research team and resolved in order to achieve a coding consensus and to ensure robust analysis.

7.3.8 Timetable

Starting qualitative work in month 9 when trial is up and running

- Set up project - 1 month
- To sample patients, conduct interviews and start data analysis - 12 months
- To complete data analysis and develop descriptive accounts of themes - 3 months
- Report writing and dissemination - 2 months

Total – 18 months

7.4 Case report forms (CRFs)

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

7.4.1 Baseline CRF (including diagnostics assessments and surgical decision)

- Patient contact details, demographics
- Urine flow rate (Qmax) and post void residual volume (PVR) data
- Date of admission and testing
- Resource use
- GP contact details
- Blood parameters
- Discretionary tests
- Procedures and duration
- Complications

7.4.2 Perioperative CRF (from surgical admission through to discharge)

- Perioperative data including date of admission and operation
- Operative procedures

- Resource use
- Pain relief, infection, complications
- Complications
- Date of discharge

7.4.3 Surgical follow up CRF (4 month postoperative urinary flow test)

- Urine flow rate (Qmax) and PVR
- Details of any other treatment actually received since surgery
- Complications

7.4.4 18 months post randomisation

- Urine flow rate (Qmax) and PVR
- Bladder diary
- Questionnaires
- Details of actual treatment received since becoming involved with the study *(or surgery, where applicable)*

7.4.5 Medical record abstraction

Information Technology (IT) or similar Departments in all sites, where the study has research governance approval, will be contacted to provide, if possible, electronic information in relation to inpatient stays, outpatient visits or any other type of hospital use that the participant has had during the 18 months of follow-up. If Hospital Patient-linked information costing systems cannot be accessed to obtain this information then at 18 months follow-up, in-patient stays, out-patient visits and procedures relating to the man's urinary symptoms, identified though the 18 month resource use questionnaire occurring in the treating hospitals, will be abstracted from the patients' medical records. In such a way that the resource use collected can be costed using NHS tariffs.

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.

The clinical data will be collected on paper*. All data will be entered onto a secure database by a member of the UPSTREAM Office Team. Personal details and administrative data will be entered onto a secure database held on a University of Bristol server, and non-identifiable data will be entered onto a secure web-based database (REDCap [Research Electronic Data Capture]). This will be entered by a member of the UPSTREAM Office Team via a secure internet link maintained by University of Bristol Information Services.

Data collected on the paper case report forms (CRF) at study centres or as questionnaires from participants will be identifiable only by participant study number (excluding the 'Personal Contact Details' section of the Baseline CRF). Recruitment centres will be responsible for the secure transfer of paperwork by post to the UPSTREAM study office where it will be stored in a secure locked cabinet in a locked room. Critically, **data containing patient identifiable information (e.g. written informed consent form and Baseline CRF) should be posted via Recorded Delivery (at least) using tamper-proof packaging that is marked 'Private and Confidential', and to the attention of a named trial team member.** The UPSTREAM Office Team will provide the tamper-proof packaging supplies, and encourage *all* patient data be transferred via this secure method.

Trial specific guidelines regarding document transfer will be provided to all centres and should be adhered to. Failure to do so would result in a protocol deviation.

Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to UPSTREAM study staff.

** Some participants may request to complete the questionnaires online, rather than via paper copies; in such cases these will be completed directly onto a secure web-based database by the participants.*

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

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

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

We decided that the important consideration is that the group of men randomised to having urodynamics should have clinical outcomes which are not inferior (rather than equivalent) to those who are randomised to management without urodynamics. This is because the likely reduction in surgery rates in the former group due to more accurate diagnosis should not disadvantage them in terms of clinical improvement. We therefore calculated our sample size based on both the primary outcome and surgery rates: non-inferiority of symptoms at 18 months after randomisation; and a reduction in surgery rates in the intervention arm.

In Bristol, audit data for 5670 men presenting with lower urinary tract symptoms suggestive of poor or obstructed urine flow show that 73% to 83% would have surgery. If an invasive urodynamics test was conducted on the same men, the data indicate that surgery would only be carried out in 60%, based on the prevalence of impaired bladder contractility contraindicating surgery. Using the more conservative difference we expect the intervention to reduce surgery from 73% in non-urodynamic assessment to 60% in the intervention arm. A two group continuity corrected chi square test with a 5% two-sided significance level will have 90% power to detect such a difference if the sample size in each group is 291.

Symptom scores will potentially improve for those men in both arms who undergo appropriate surgery. For the men in the non-urodynamic assessment arm incorrectly presumed to have outlet obstruction (due to less comprehensive testing) who nevertheless undergo surgery, published research suggests there may be some degree of symptom improvement Symptom scores of the non-operated men in both groups should be similar. Symptomatic outcome of surgery is confounded by a number of factors for which we cannot control. These include:

- Long-standing BPO might impair bladder contractility, reducing the symptom benefit of surgery.
- BPO-relieving surgery increases the calibre of the outlet channel regardless of whether BPO is present, and this might improve urinary stream in men who technically did not have BPO.
- A "placebo effect" is known to arise both from clinical contact and from the surgical procedure.
- Whilst voiding LUTS (obstruction) typically improves after surgery, this advantage will be offset in some men due to deterioration in storage LUTS (e.g. incontinence, overactive bladder).

We therefore anticipate the overall IPSS at 18 months in both arms might be similar despite group differences in surgery rates.

However, to ensure that the men in the urodynamic arm are not disadvantaged by the reduction in surgery rates, we need to ensure that the primary outcome, symptom score, has adequate power to rule out non-inferiority. Therefore, assuming no difference between the groups, a trial of 310 men per arm will give 80% power to rule out a non-inferiority margin of 1 point below the mean IPSS in the non-urodynamic arm, using a one-sided t-test (common standard deviation of 5) at the 5% significance level.

The sample size calculation is based on the consideration that men randomised to urodynamics should have clinical outcomes which are not inferior (rather than equivalent) to those who are randomised to management without urodynamics. For the Primary outcome, a difference in LUTS score of 1 point (on IPSS scale) is considered non-inferior. The team felt that a 1 point non-inferiority margin was appropriate for the following reasons:

- A difference of 3 points and 0.5 points on the total IPSS score and QoL IPSS score respectively indicates a minimally clinical important difference (MCID) for overall urinary condition ((Barry *et al*, 2013). While this is the case for the overall IPSS score a difference of <3 may involve substantial changes in symptom bother associated with certain subscales (Agarwal *et al*., 2014), especially in relation to storage-type LUTS.
- One void per night does not generally prove a problem for patients whereas two or more is considered substantially 'bothersome' by most patients. Given that a 1 point difference on the IPSS scale could indicate a difference in nocturia of 2 to 1 we would consider this to be a significant turning point on the IPSS scale (Tikkinen *et al*., 2009).
- The trial team feel that a 1 point difference is a conservative estimate and, given this, will avoid false claims of non-inferiority.

Loss to follow-up in our previous trial of conservative treatment for men with urinary incontinence after prostate surgery (Glazener *et al.*, 2011) was 5 to 10% at one year. However, a more conservative estimate of just over 20% loss to follow up has been used in the sample size calculations. Therefore sample size will be 310 per arm, and 388 per arm to take into account 20% loss to follow-up. Our recruitment target will be 400 per arm with the aim of achieving no less than 388 per arm at 18 months follow-up.

9.2 Statistical Analysis

The primary outcome will be the International Prostate Symptom Score (IPSS) which consists of 7 questions concerning urinary symptoms with a 6 point Likert scale response from 0-5. The total IPSS score will thus range from 0 to 35. This will be evaluated using linear regression; the symptom score at 18 months being the dependent variable tested against the treatment arms along with baseline IPSS score as a covariate. For those with missing baseline scores, the 6 month

IPSS score may be used as a substitute unless urodynamics has been conducted prior to the 6 month questionnaire. To assess non-inferiority of IPSS the post-treatment difference at 18 months between the two arms will be used with a non-inferiority margin of 1.0. Between-centre effects will be examined and a mixed model approach with treatment group as a fixed factor and investigational site as a random effect will be considered. Differences between the arms at baseline will be investigated and anything in excess of 0.5 standard deviations or a difference of 10% or more will be controlled for in a sensitivity analysis. Other symptom scores such as the ICIQ-MLUTS, which is potentially more sensitive but less widely recognised, will be evaluated in a similar way as a secondary outcome, adjusting for baseline scores. Acute urinary retention as a possible complication will also be examined as secondary outcome.

All analyses will be based on the intention-to-treat principle, analysing men in the groups to which they were randomised. The primary analysis will be based on the observed data supported by a sensitivity analysis where all missing data will be imputed at baseline using appropriate imputation methods and a range of assumptions. Missing items on the health-related outcome measures will be treated as per the instructions for that particular measure and imputed if necessary. In addition, a complier average causal effect (CACE) analysis will be performed to allow adjustment for non-compliance. All outcomes will be described and compared with the appropriate descriptive statistics where relevant: mean and standard deviation for continuous and count outcomes, or medians and inter-quartile range if required for skewed data; numbers and percentages for dichotomous and categorical outcomes (for example 'Did the man have a PSA test?').

This brief outline of the analysis will be developed into a statistical analysis plan that will be agreed in advance by the Trial Steering Committee and the Data Monitoring Committee. All primary study analyses will then be conducted according to that plan.

9.2.1 Planned further analyses

Full details of all analyses will be included in the UPSTREAM Statistical Analysis Plan. Subgroup analysis will be carried out for the primary analysis (IPSS score) and the main secondary analysis (surgery rates). Formal tests of interaction between the potential effect modifiers and treatment pathway will be carried out to test whether treatment effect differs between the different sub groups. The potential effect modifiers are age, flow rate (>12ml/s vs. ≤12ml/s), maximum voided volume (<200ml vs. ≥200ml), nocturia (Yes vs. No) and severity of storage LUTS (more substantial vs. less substantial).

9.2.2 Proposed frequency of analyses

Men will be followed up at 6 months (by post), 12 months (post), and 18 months (clinic), after randomisation. Men undergoing surgery will also attend clinic for flow rate testing 4 months after operation. They will be asked to consent to longer term follow up although this is not funded in this application. The main analysis will be performed when all 18 month follow up has been completed. An independent Data Monitoring Committee will review confidential interim analyses of accumulating data at its discretion.

9.3 Economic evaluation

The trial will include a formal economic evaluation comparing the costs and cost-effectiveness of the interventions from the perspectives of the NHS, Personal Social Services and patients. 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. over the counter medication) will be estimated through the collection of resource-use data as outlined earlier and the valuation of these data.

NHS tariffs will be used to quantify the resource use information contained in the CRFs. . All other resource use will be valued using routine sources and information from the patients themselves.

Differences in costs between the arms from each of the 3 perspectives will be evaluated using regression techniques adjusting for pre-specified baseline characteristics, randomisation variables and a centre effect. The same model specification will be used to evaluate the differences in QALYs.

For each of the three perspectives the difference in costs and in effectiveness in terms of surgery rates and IPSS scores will be examined. If neither arm is dominant i.e. both cheaper and more effective, then incremental cost-effectiveness ratios will be calculated in relation to surgery rates and IPSS scores. The differences in costs and QALYs will be examined using 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 for all these analyses will be addressed using cost-effectiveness acceptability curves and sensitivity analyses. One aspect of uncertainty is likely to be that of missing data. In order to address this, a pre-specified analysis plan will be created in which the plausible assumptions about missing data will be created. These assumptions will then be tested within the sensitivity analyses.

9.4 Recruitment rates and expected throughput per centre

Important notice: Delays in centres being ready for the trial and additional work to improve recruitment amongst centres that were ready meant the initial window to assess whether we were meeting our recruitment target (feasibility phase) was too narrow. Initially the window was to assess a target of 48 patients but delays and a more realistic assessment of recruitment meant a revised target of 17 patients of which we recruited 13 patients. The Trial Steering Committee (TSC) met in January 2015 and approved a revised timescale (Feb-Apr 2015) and revised target (42 patients from 4 centres) for the feasibility phase, with additional reporting to the TSC upon conclusion. As such a revised recruitment plan for the study was devised. Details of the original recruitment plan can be seen in Appendix 2.

9.4.1 Revised recruitment plan and underlying assumptions

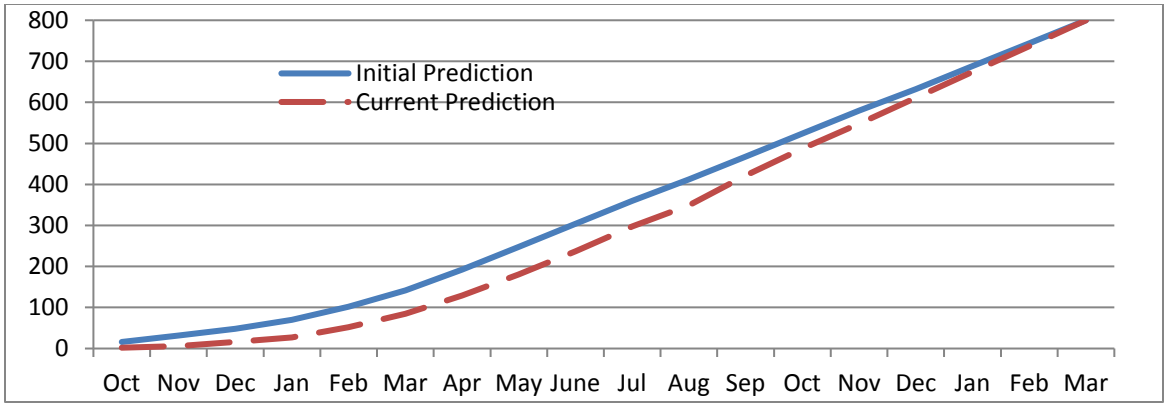
The initial cumulative accrual prediction was based on a relatively simple linear trend assumption without incorporating differential recruitment over time by centres or different recruitment rates within centres. Therefore, we have revised the accrual projections (at the request of the TSC) based on a more realistic assumption conditioned both on differential recruitment by centres over time and recruitment capacity.

9.4.2 Revised model assumptions for trial sites

I. Recruitment for the first month after a centre opens is 1 participant
II. Recruitment for the next two months will be 2 participants
III. Steady state subsequently will be 3 participants for 17 centres until the completion of accrual target
IV. At two centres (Bristol and Exeter) we anticipate higher recruitment rates; this will be 2 participants in the first month after opening, 3 in the next 2 months, 4 in the next 3 months, 5 until September 2015 and 6 until the completion of accrual

9.4.3 Impact of the revised conditional recruitment model on overall accrual

The figure below plots the original predictions for accrual (y axis participant recruited) (initial prediction: blue line) and the revised prediction (current prediction: orange, dashed line) against the study timeline along the x axis from October 2014 until March 2016 (planned completion of recruitment). The plotted values for October to December 2014 are actual accrual for the current prediction model.



9.4.4 Impact of the revised recruitment model during the second feasibility phase at four sites

The original feasibility phase planned for 48 participants recruited from 4 centres between October and December 2014 (i.e. 4 patients x 4 sites x 3 months). At the end of December the four centres had achieved 8 of the 12 projected months of recruitment; so should have recruited 32 patients under the original plan, but actually recruited 13 patients (41%). Our revised model projected 17 patients recruited between October and December, so the actual recruited in that period represents a shortfall of around 25% which is accommodated in the overall accruals shown in the figure above.

The TSC will expect 42 more participants recruited at four centres during the second feasibility phase (February – April 2015) as an indicator that trial recruitment will be delivered according to original timelines.

10. Project timetable and milestones

The projected start date is 1 April 2014, and the study duration will be 54 months, to 30th September 2018. Milestones are: pre-funding: multicentre research ethics and central R&D approvals, set up office, assemble team, and establish first four five centres, months 1-6; run feasibility study and establish study in all centres, months 7-17; identify and recruit 800 participants, months 7-33; follow up (including 4 month post-operative follow-up to 18 month follow-up) months 11-52; analysis and dissemination of outcomes, months 43-54. Draft final report due to funder 18th October 2018. Milestones for the qualitative component are months 9-25, set up qualitative work; month25-36, sample patients, conduct interviews and start data analysis; month 34-42, complete data analysis, develop descriptive accounts of themes, report writing and dissemination. Trial Complete 30th September 2018 (Appendix 2).

** **Important notice:** The timelines above follow a Trial Steering Committee (TSC) met on 31st March 2016. Further to that meeting and after gathering feedback from the Independent Data Monitoring Committee, the TSC reviewed and gave their full support for a six month cost extension request which has now been approved by the NIHR HTA.*

11. Organisation

11.1 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 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.

11.2 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 UPSTREAM Study Office;
- keep local staff informed of progress in the trial;
- contact potential participants by: providing the Patient Information Sheet and Assessment Information Sheet to men; identifying any eligible; 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 screening log of whether eligible men are recruited or not (with reasons for non-participation);
- collect baseline data describing the men, 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 UPSTREAM database or telephone;
- ensure operative and postoperative data are collected and recorded in the UPSTREAM documentation, 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.

11.3 Patient Panel (PP)

The PP will meet prior to study start to advise on all the trial documentation and in particular the patient information leaflet and the randomisation process. We will suggest they meet with the CI every 3 months or more often if needed.

11.4 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. The Study Administrator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data). 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 BRTC Quality Assurance Manager will oversee and demonstrate that BRTC's standard operating procedures for trials have been followed and properly documented, including observance of GCP throughout.

The UPSTREAM Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting.

11.5 Project Management Group (PMG)

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

11.6 Trial Steering Committee (TSC)

The role of the TSC is to monitor and supervise the progress of the trial. The Chairman will be Prof. Mark Emberton, Professor of Urology at University College London. The TSC will have at least two other independent members, and will include the Trial Manager (Dr Amanda Lewis or Dr Helen Winton) and the Chief Investigator (Mr Marcus Drake). The Patient Panel of service users and the HTA will be invited to nominate a representative to sit on the TSC. Other non-voting members will include the grant holders. 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.

11.7 Data Monitoring Committee (DMC)

The DMC will also have an independent chair (Mr Matthew Sydes, Senior Scientist and Senior Medical Statistician at University College London), 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. We propose using the DAMOCLES charter for IDMCs as our reference point, which will be agreed in advance by the TSC. It is anticipated that both the TSC and the DMC would meet twice a year, once face-to-face and once via teleconferencing. 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 will obtain approval from the South Central – Oxford 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 serious 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 will be asked to consent to being interviewed to explore reasons for non-randomisation.

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. 12/140/01).

13. Publication policy

The success of the study depends entirely on the wholehearted collaboration of a large number of men undergoing investigation for 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 UPSTREAM 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 UPSTREAM 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 UPSTREAM 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 UPSTREAM 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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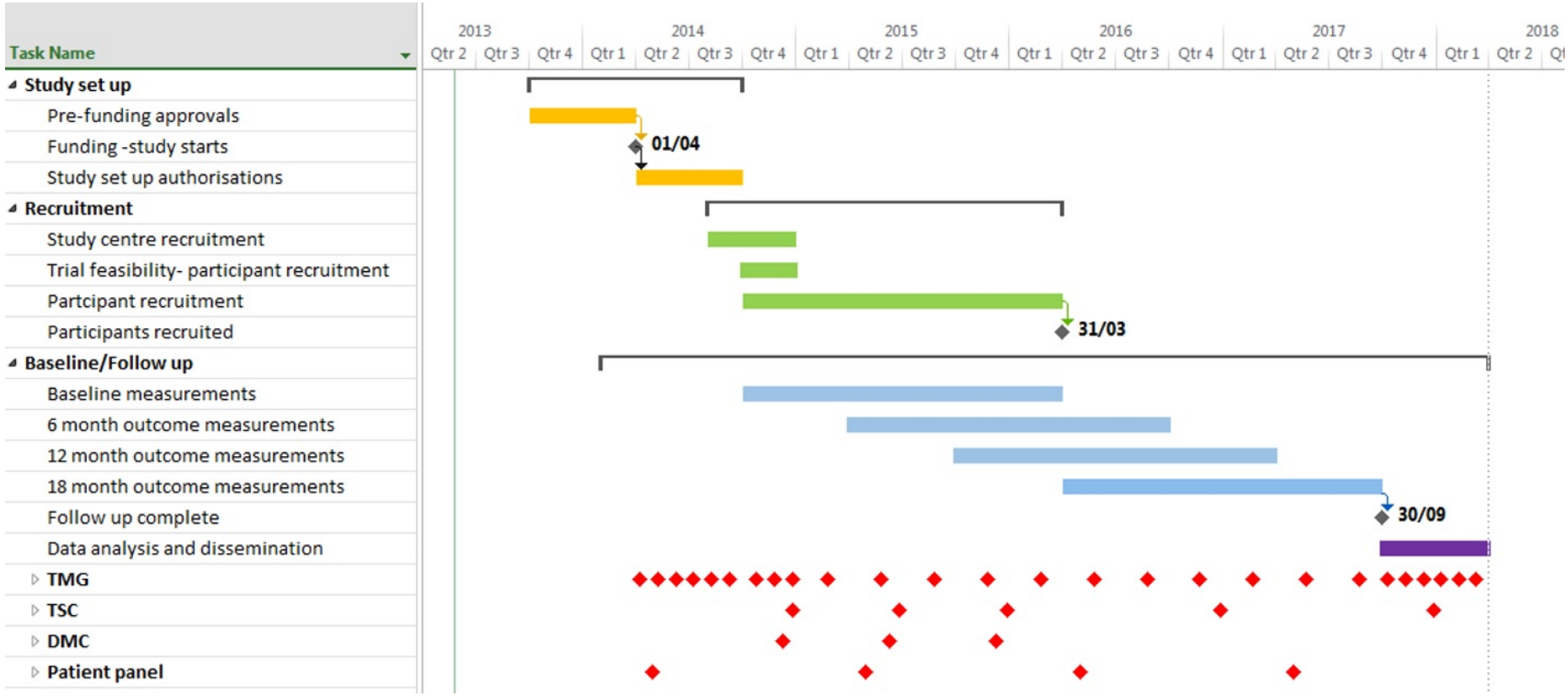
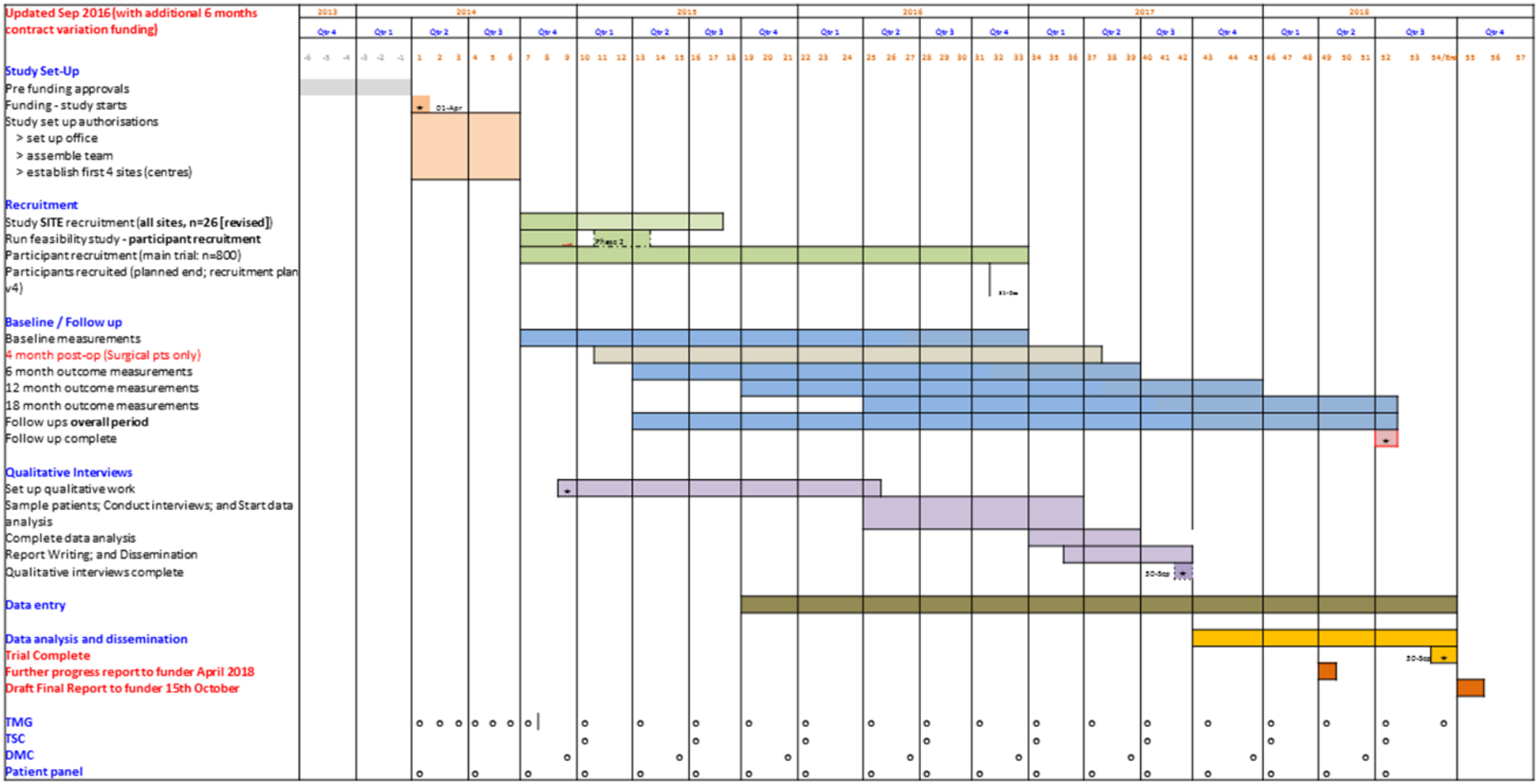
15. Appendix 1. UPSTREAM gantt chart



** **Important notice:** A meeting with the Funders and TSC Chair in July 2015 approved a revised recruitment schedule, such that recruitment would continue for 3-months longer than originally proposed (i.e. extend from end of March 2016 to end of June 2016). The follow-up period would also, therefore extend for an additional 3-months (i.e. until end of December 2017).*

16. Appendix 2. UPSTREAM Gantt Chart as constructed September 2016



17. Appendix 3. Original recruitment plan

The proposed 18 month recruitment period is based on a throughput of approximately 120-450 eligible patients per site per year in 14 sites (estimated 3,800 patients), of whom we estimate 50% (1,900) will be eligible. Our previous studies suggest a recruitment rate of over 50% in eligible patients, but we have conservatively powered for 40% to consent to randomisation (n=800). We assume that some eligible patients will be missed in the first month after initiation and also in August and December due to staff holidays.

The internal feasibility pilot will use data from the four selected centres (Bristol, Kingston-upon-Thames, Newcastle and Taunton), concluding when 12 site recruitment months have been completed (end of month nine). Proportionately, this should yield 48 subjects out of the overall accrual target of 800.

Projected accrual is shown in the Figure. The TMG will monitor the recruitment rate trajectory to ensure that it is consistent with meeting the overall accrual rate required for the full study. Actual accrual will be compared with projected at all stages, and measures put in place if required to ensure completion of recruitment, including activation of additional centres if needed.

Participant recruitment projection
Number of men recruited (y-axis) is plotted against recruitment month (x-axis). Recruitment month 1-3 is the feasibility phase (equating to trial months 7-9).

18. Appendix 4. Revised recruitment plan