TReatIng Urinary symptoms in Men in Primary Healthcare using non-pharmacological and non-surgical interventions (TRIUMPH)

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TRIAL SUMMARY

Trial Title	TReatIng Urinary symptoms in Men in Primary Healthcare using non-pharmacological and non-surgical interventions	
Short title	TRIUMPH	
Trial Design	A two-arm cluster RCT randomising GP practices to treat men with lower urinary tract symptoms (LUTS) between a care pathway based on manualised and standardised active management (Intervention arm) and one based on current management ("Usual care" Comparator arm).	
Trial Participants	Adult men diagnosed as having LUTS by their GP	
Planned Sample Size	840 patients from at least 24 practices	
Treatment duration	3 months	
Follow up	6 and 12 months after enrolment	
Planned Trial Period	Recruitment between 1/05/2018 and 30/04/2019 Continue treatment and follow-up until 01/05/2020	
	Primary	Secondary
Objectives	To determine whether manualised and standardised care intervention achieves superior symptomatic outcome versus usual care for LUTS measured by the overall IPSS score at 12 months after consent	To compare manualised and standardised care intervention to usual care in relation to: • Disease-specific quality of life (6 & 12 months) • Symptoms (6 & 12 months) • Cost effectiveness • Harms • Use of NHS resources • Overall quality of life and general health • Acceptability of assessment and provision of care • Change in patient perception of their LUTS condition
Outcome Measures	Patient reported outcome (IPSS) at 12 months	● LUTS/ QoL at 6 & 12 months (ICIQ-UI SF, IPSS); ● self-perception at 6 & 12 months (B-IPQ); ● Referrals to GP/ secondary care; ● Adverse events of treatment; ● Cost effectiveness (EQ-5D)

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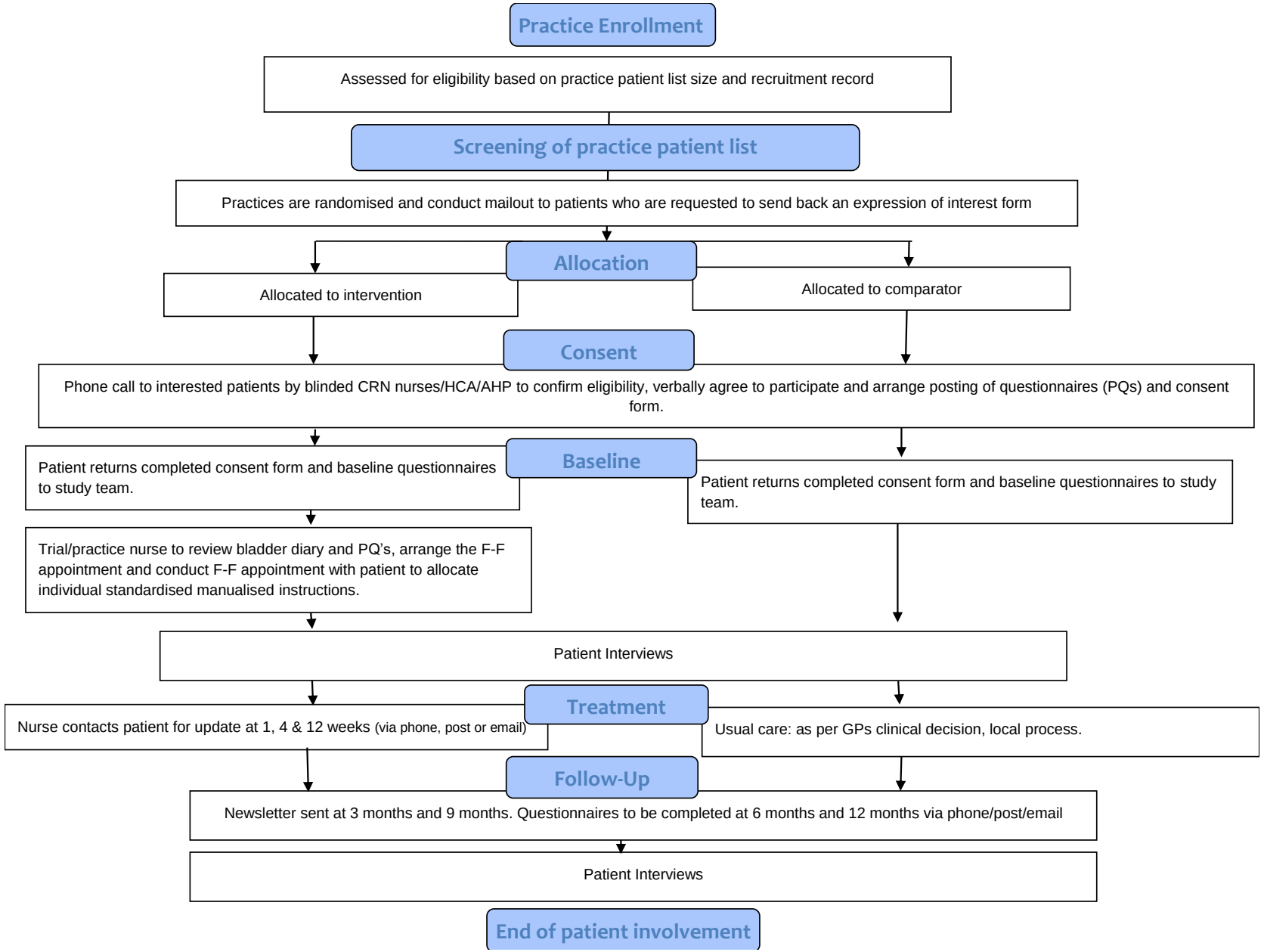
LIST OF ABBREVIATIONS

AE	Adverse Event
AHP	Allied Health Professional
BAUS	British Association of Urological Surgeons
BPE	Benign Prostate Enlargement
BRTC	Bristol Randomised Trials Collaboration
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
EAU	European Association of Urology
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HCA	Health Care Assistant
HCP	Health Care Professional
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRQOL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form
IPSS	International Prostate Symptom Score
ISF	Investigator Site File

ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
LUTS	Lower Urinary Tract Symptoms
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
OAB	Overactive Bladder
PAG	Patient Advisory Group
PI	Principal Investigator
PIL	Participant Information Leaflet
PPI	Patient and Public Involvement
PQ	Patient Questionnaires
QALY	Quality adjusted life year
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
B-IPQ	Self-Assessment Goal Achievement
SAP	Statistical analysis plan
SLA	Service Level Agreement
SOP	Standard Operating Procedure
SUR	Seemingly Unrelated Regressions
TMF	Trial Master File
TMG	Trial Management Group
TPB	Theory of Planned Behaviour
TSC	Trial Steering Committee
UoB	University of Bristol

INTERVENTION AND COMPARATOR FLOW CHART



STUDY PROTOCOL

TReatIng Urinary symptoms in Men in Primary Healthcare using non-pharmacological and non-surgical interventions

1 BACKGROUND

Normal urinary tract function reflects the need to store urine for most of the day. People also occasionally need to empty the bladder ("voiding"), either because it feels full, or because they anticipate difficulty getting to the toilet in the near future. This normal alternation between storage and voiding allows categorisation of the lower urinary tract symptoms (LUTS). LUTS related to problems with storage include increased daytime urinary frequency, nocturia (waking at night to pass urine), urgency and incontinence. LUTS related to problems with voiding include slow stream, intermittency, hesitancy, straining and dribbling; in addition, there are symptoms consistently happening straight after voiding ("post-voiding LUTS"), e.g. post-voiding dribble and sensation of incomplete emptying.

LUTS can be caused by prostate enlargement or bladder dysfunction. Behavioural tendencies among men may also influence their likelihood of experiencing problems. In broad terms, the influential processes are:

1. Benign prostate enlargement (BPE); enlargement of the prostate gland, leading to compression or distortion of the urethra, which hampers bladder emptying. This is a key factor in generating voiding LUTS.

2. Urethral pooling; the urethra is the anatomical tube that carries urine from the bladder at the time of voiding. In men, it has an expanded section known as the urethral bulb, just below the continence muscle (the sphincter). This can be a site of urine accumulation, notably in men with BPE, which is a key cause of post-voiding dribble.

3. Bladder dysfunction; ageing influences bladder function, giving rise to overactive bladder (OAB) syndrome (presence of urgency, increased daytime frequency and nocturia). This is a key contributor to storage LUTS.

4. Fluid intake; the volume and type of fluid intake is highly influential to voiding frequency (day and night) and may be a factor in urgency. This is another key contributor to storage LUTS.

Ninety percent of men aged 50 to 80 years suffer from at least one LUTS. Prevalence and severity increase with age (1) and the progressive growth of the aged population group has emphasised the importance to our society of appropriate and effective management of male LUTS. For many men,

symptoms badly affect quality of life, occupation and other activities; such problematic LUTS are described as “bothersome” according to the impact on the patient.

To understand the impact, we undertook a literature review (2) and evaluated the baseline data and qualitative assessments undertaken in the UPSTREAM study (Urodynamics for prostate surgery: randomised evaluation of assessment methods (3). Both the literature review and UPSTREAM findings identified that the important LUTS are: urgency/ urgency incontinence, post-voiding dribble, nocturia and increased frequency.

NICE Clinical Guideline 97, (4) “The management of lower urinary tract symptoms in men” sets out aims to improve the quality of life (QoL) for men with LUTS by recommending which assessments they should receive, and when conservative management, drug treatment and surgery can help (5) . This requires exclusion of serious medical conditions, malignancy and urinary tract infection, and the impact of their LUTS symptoms (voiding/ post-voiding/ storage) should be checked.

The European Association of Urology (EAU) Guidelines on Male LUTS, (for which the TRIUMPH Chief Investigator (CI) is a panel member), has undertaken systematic reviews of assessment and therapy of male LUTS (6) (7). Summaries of these systematic reviews were published in European Urology. They state that categorising the precise symptoms is an expectation of urological practice. Conservative treatment measures (fluid advice, bladder training, urethral compression and release, and pelvic floor muscle exercises) are stipulated by the EAU Guidelines (7).

The assessment expectations described these urological guidelines as relatively time-consuming for a GP consultation. Thus, many men undergo somewhat limited assessment (see experience from the UPSTREAM trial below) mainly to exclude serious underlying conditions. Furthermore, the evidence to support conservative interventions is limited. The Cochrane review on lifestyle interventions for the treatment of urinary incontinence in adults (8) suggested there is insufficient evidence to justify fluid advice training for treatment of urgency incontinence. In primary care, it appears to be common that men may simply receive a prescription of medications to treat the prostate, such as an alpha-1 adrenergic antagonist (“alpha-blocker”).

Men usually present with a range of LUTS. Disease-specific, Health-related quality of life (HRQOL) measures are significantly worse in men with higher symptom frequency and severity ratings than in men with low symptom frequency and severity ratings in population-based studies (9).

When we reviewed UPSTREAM study (HTA 12/140/01) baseline data of the referrals from primary care to secondary care, we found that primary care use of symptom scores and bladder diaries (which

are recommended for use in primary care by NICE guidelines) were below 10%. Alpha blocker use was approximately 80%. We also found;

a) 66% of men had urinary urgency ("sometimes", "most" or "all of the time"), 88% of whom rated it as being of moderate or severe bother

b) 30% of men had urgency urinary incontinence, 95% of whom rated it as being of moderate or severe bother

c) 41% of men had increased urination frequency, 89% of whom rated it as being of moderate or severe bother

d) 34% of men had post-voiding dribble, 93% of whom rated it as being of moderate or severe bother

e) 77% of men had nocturia at least twice per night, 85% of whom rated it as being of moderate or severe bother

The majority of these men required conservative interventions as part of their therapy in the UPSTREAM study, and 23% of referrals to secondary care may have been preventable. Thus, the current pathway is at risk of poor outcomes, persistent symptoms and avoidable referrals for men.

An NHS Evidence Update indicated that self-management may have a role in the management of LUTS (10), citing a post-hoc analysis (11) of a single centre RCT (12) of 140 men with LUTS assigned to a self-management programme plus standard care or standard care alone. Better voided volumes, daytime frequency and nocturia were reported in the intervention arm. The study had a relatively small patient population and was conducted in a single tertiary treatment centre. The study did not affect NICE CG97 (4), and indicated that a multicentre RCT would be needed to see if these results could be replicated in everyday clinical practice. TRIUMPH has the potential merit of exploring the means to introduce self-management of LUTS into clinical care, and the plan to undertake the study in the primary care setting reflects an NHS priority to reduce hospital referrals.

2 RATIONALE

Of the adult population, 1.5-3% present to their GPs each year with LUTS. 44,000 new cases of symptomatic BPE are diagnosed each year. Since LUTS increase with ageing, the number of patients affected is likely to increase by almost 50% by the year 2025, in line with population ageing. In a Quality and Productivity Proven Case Study, the costs saved by reducing inappropriate referrals to secondary care were £21,652 per 100,000 population (Improving the quality of care for men with lower urinary tract symptoms: shared decision making. South Norfolk Healthcare Community Interest Company).

TRIUMPH addresses the HTA commissioning brief, by investigating the research question "What is the clinical and cost-effectiveness of non-pharmacological and non-surgical interventions to treat men with lower urinary tract symptoms (LUTS)?" TRIUMPH will randomise GP practices to treat men with bothersome LUTS between the specified intervention (non-pharmacological and non-surgical interventions) and comparator (usual care alone) and is powered to ascertain clinically meaningful differences in symptom outcomes at one year.

The NICE Quality Standard (13) and NICE Pathway specify the need to offer conservative interventions to men with storage or voiding LUTS. Non-pharmacological therapies, such as bladder training drills, pelvic floor exercises and release techniques, may be as effective as medications in some people. They are relatively non-invasive and have a low risk of adverse events. Qualitative interviews with men in the UPSTREAM study indicate men are supportive of such measures in their treatment plan.

First line treatment is conservative, comprising of education on the nature of the complaint and interventions aimed at counteracting the contribution to LUTS of incomplete bladder emptying (double voiding), urgency (pelvic floor muscle exercises, bladder training), urinary frequency and nocturia (fluid advice), post-void dribble (urethral "milking", meaning compression and release).

There is a growing body of literature regarding exploration of the qualitative perspective among those involved in randomised controlled trials to aid interpretation of the quantitative findings. To our knowledge no studies to date have explored patient and clinicians' views regarding primary care interventions for LUTS. TRIUMPH will include a qualitative component to evaluate patients' attitudes and experiences in the intervention arm and will explore patients' overall LUTS experience for the usual care arm. Clinicians in both arms will be interviewed at baseline and during the recruitment phase of the trial in order to capture the variability of the practice populations in both usual care and intervention practices involved, as well as perspectives on the intervention and recruitment processes.

Interview participants will also be sought from those who decline to take part in TRIUMPH in order to explore their reasons for declining and potential barriers to recruitment.

An abstract (14) quoted by NICE (4) as saying that 23% of local GPs reported offering frequency volume charts and 50% use a validated symptom score. However, these data were derived from direct enquiries to GPs.

In order to facilitate the delivery of active management, we reviewed limitations of the current pathway in consultation with patient users and GPs, and through the UPSTREAM trial. Several key issues were identified which currently reduce the ability of GPs to offer conservative therapy:

1. Short duration of GP consultations
2. Several different LUTS are often present in each individual
3. Early use of drug prescriptions without addressing key non-pharmaceutical conservative interventions
4. Lack of suitable written materials describing conservative interventions
5. Lack of time from healthcare professionals (HCPs) to provide support and guidance of personally-relevant conservative intervention(s) of benefit to individual patients
6. The requirement that HCPs have complete confidence in the efficacy of conservative interventions

A key element to the success of the trial will be the patient's adherence to the intervention. The self-regulation model of illness (15) will be used to assess men's self-management of their LUTS. This model proposes that the presence of a health threat activates cognitive and emotional perceptions of the threat. In particular, cognitive representations or 'illness perceptions' guide coping strategies. For example, a man who perceives his LUTS as more threatening (e.g. his symptoms will severely affect his life over a long-term period of time) may want to take action to mitigate the threat (e.g. use advice from GP). Such actions may lead to improved health-related outcomes (e.g. better symptom-management, reduced emotional distress). Illness perceptions also provide a benchmark for individuals to assess how well they are managing their condition over time. For example, the same man may change the way he perceives and copes with his LUTS after choosing to ignore the advice provided by his GP and experience no improvement in his symptoms. Illness perceptions can be measured using a self-report questionnaire. Here, we plan to use the Brief Illness Perceptions Questionnaire (B-IPQ) (16) , which will be administered at baseline, 6 and 12 months follow-up to both the intervention and control. We will observe associations between illness perceptions and the intervention as well as observe changes in illness perceptions at follow-ups and between trial arms.

LUTS is a composite of different symptoms and each symptom has predictable components that can be targeted with specific educational information and active management, i.e. Standardised. The nurse or healthcare assistant will tailor specific actions for each patient, in conjunction with the patient, to suit their symptom needs, bother of these symptoms and impact on quality of life. This will be implemented through a Manualised approach - the patient will be directed to the standardised information applicable to their LUTS in the patient booklet based on their symptom score and bladder diary findings. The manualised approach will be nurse/healthcare assistant delivered, as patients desire information provided face-to-face by trained health care professionals. Subsequently, we refer to the intervention as “Manualised and Standardised Care”.

TRIUMPH will deliver an approach that aims to ensure a more efficient and effective delivery in primary care by addressing the key limitations of the current pathway as follows:

a) Use of symptom scores and bladder diary to identify the range of LUTS present in an individual. We propose to use the IPSS due to its wide use and familiarity. It will be supplemented by the International Consultation on Incontinence Questionnaire Urinary Incontinence-Short Form (ICIQ-UI-SF), since incontinence is not covered by the IPSS. We will also use the ICIQ Bladder Diary (17) .

b) Production of effective written materials

c) Training of HCPs in the interpretation of symptom scores and the merits of active management related to TPB. We plan to include a 2-hour training session for practices allocated to the intervention arm. This will be for participating HCPs (predominantly practice nurses/healthcare assistants) during site set-up.

Thereby, GP consultations in the future will be able to focus on exclusion of serious conditions and place less reliance on early drug prescription.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Aim: To determine whether a care pathway including manualised and standardised application of non-pharmacological and non-surgical interventions is superior to usual care, in terms of symptom severity at one year after consent.

3.1 Primary objective

To determine whether manualised and standardised care intervention achieves superior symptomatic outcome versus usual care for LUTS measured by the overall IPSS score at 12 months after consent.

3.2 Secondary objectives

To determine:

a) Whether manualised and standardised care intervention achieves superior disease-specific quality of life outcome for LUTS measured by the IPSS Quality of Life score at 6 and 12 months after consent
b) Whether manualised and standardised care intervention achieves superior symptomatic outcome for LUTS. This will be measured separately by the overall IPSS score at 6 months after consent and ICIQ-UI-SF at 6 and 12 months
c) The cost effectiveness of LUTS management pathways, measured using quality-adjusted life-years (QALYs) and the primary outcome at 12 months after consent
d) The relative harms of the two pathways
e) The differential use of NHS resources
f) The differential effects on other outcomes, such as overall quality of life and general health
g) The acceptability of assessment and provision of care.
h) Change in patient perception of their LUTS condition in the two management pathways

3.3 Primary endpoint/outcome

The primary endpoint will be patient reported outcome (IPSS) at 12 months after consent. We hypothesise that in men with bothersome LUTS, manualised and standardised application of non-pharmacological and non-surgical interventions improves LUTS severity, compared to a pathway of men undergoing usual care. The primary clinical outcome, the IPSS, is validated, extensively tested in LUTS research, and widely employed in urology services.

3.4 Secondary endpoints/outcomes

- LUT specific QoL at 6 & 12 months (IPSS QoL); (objective a)
- Symptoms scores at 6 months (IPSS overall score) and 6 & 12 months (ICIQ-UI-SF) (objective b)

- Cost-effectiveness analyses from an NHS perspective. The EQ-5D-5L will be used to calculate QALYs (objective c)
- Number of Adverse events (e.g. infection, urinary retention) (objective d)
- Number of GP consultations (objective e)
- Number of referrals to secondary care (objective e)
- Overall quality of life measured by the EQ-5D-5L (objective f)
- A qualitative element of the research study will evaluate patient experiences of intervention (objective g).
- Patient perception of their LUTS; Brief Illness Perception Questionnaire (B-IPQ; 16) (objective h)

3.5 Measurement of clinical outcomes

Clinical outcomes will be assessed by participant-completed questionnaires at baseline (postal), 6 months (telephone, online or postal) and 12 months (telephone, online or postal), which will be completed by all participants. A case report form will be completed at the time of baseline assessment, during the 12-week treatment phase (intervention participants only) and follow up at 12 months, providing details of the treatment, adverse events and resource use. We are using standardised outcome instruments. The components and timing of follow-up measures are shown in Table 1.

3.5.1 Economic outcome measures

Intervention related resources used in the intervention arm (e.g. nurse time) will be collected on study designed proformas. At 12 months follow-up, healthcare resource use including medications, GP practice visits and secondary care attendances will be extracted from all participants' primary care medical records. The EQ-5D-5L will be administered to all men at baseline, 6 and 12 months and will be used to calculate quality adjusted life years (QALYs)

4 TRIAL DESIGN

Two-arm cluster RCT randomising GP practices to treat men with a diagnosis of lower urinary tract symptoms (LUTS) between a care pathway based on manualised and standardised care using active management (non-pharmacological “Intervention arm”) and one based on current management (usual care “Comparator arm”).

5 STUDY SETTING

This is a multi-centre trial recruiting patients from at least 24 GP practices at two “hubs” (Bristol and Southampton) identifying patients at an early stage in the clinical pathway for LUTS and who are potentially most suited to active or conservative non-pharmacological management.

6 ELIGIBILITY CRITERIA

6.1 GP Practice Selection Criteria

Inclusion criteria

- Adequate number of eligible patients determined by pre-randomisation practice database search.

Exclusion criteria

- Unable to provide adequate treatment room space and availability for trial or practice nurse/healthcare assistant to complete HCP training and baseline visits.

Other considerations

The PRIMUS study is another study open to recruitment in primary care and relates to diagnosis of LUTS in men. However, the PRIMUS study is recruiting incident cases of men with LUTS rather than prevalent. Practices can take part in both. Patients who are incident cases and participate in PRIMUS will be eligible to participate in TRIUMPH after they have completed their involvement in PRIMUS and have allowed a three month break in between, due to the after effects of the PRIMUS study procedures.

6.2 Subject population

The subject population includes all adult men with bothersome LUTS. Prevalent cases of LUTS assessed according to NICE clinical guideline on Male LUTS (4) will be identified from practice databases by means of a standardised search of electronic medical records, using a search strategy developed by the study team based on the criteria below. GPs will screen eligible patient lists for those criteria the database search cannot account for.

6.3 Participant Inclusion criteria

Adult men (≥18) with bothersome LUTS.

6.4 Participant Exclusion criteria

- Lack of capacity to consent;
- Unable to pass urine without a catheter (indwelling or intermittent catheterisation);
- Relevant neurological disease or referral;
- Undergoing urological testing for LUTS;
- Currently being treated for prostate or bladder cancer;

- Previous prostate surgery;
- Poorly-controlled diabetes mellitus as determined by the patient's GP through screening
- Recently referred or currently under urology review
- Visible haematuria
- Unable to complete assessments in English;

7 TRIAL PROCEDURES

7.1 Recruitment, screening and consent

All eligible men with LUTS will be identified from the GP site clinical database using the database search protocol. If practices have sufficient numbers of eligible patients, practices will then be eligible for randomisation to either the Usual care or the Intervention arm. The list of potential patients will be screened for eligibility by the GPs prior to practices being allocated to treatment groups. Eligible patients will be invited by post to join the study. Practices will be provided with login details to Docmail to assist with the posting of invite letters. The invitation pack will include the Patient Information Leaflet (PIL), an expression of interest form and a pre-paid return envelope. Once the practice has screened their lists and sent the invite letters, they will be randomised centrally.

On receipt of the expression of interest, which can be completed online (via the Bristol Online Survey (BOS)) or via post (collated by the central research team), the Research Nurse/HCA/AHP from the Clinical Research Network (CRN) will phone the patient to discuss the study further. The CRN will be blinded to which arm the practices have been randomised to.

The CRN will inform the central research team which patients verbally agree to participate so they can be sent the relevant patient pack depending on which arm the patient's practice is randomised to. All patients will receive the same consent forms and questionnaires, but those in the intervention arm will also receive a bladder diary to be completed before their face-to-face visit.

For patients in the control arm, the central research team will send the consent form and symptom score questionnaires either by post or via a link to online versions for the patient to complete. For these patients, the return of the completed consent form along with the questionnaires, will demonstrate explicit consent to participate in the study.

For patients in the intervention arm, the central research team will send the consent form, bladder diary and symptom score questionnaires by their chosen medium. Once the bladder diary and questionnaires have been returned, the trial Research or Practice Nurse/Health Care Assistant will arrange an appointment for a face-to-face consultation to review the bladder diary and symptoms scores and administer the standardised manualised intervention(s) as applicable, to the individual patient.

All men who enter the study will be logged with the central trial office at the University of Bristol (UoB) and given a unique Study Number. The GP will be informed by the central study team by letter about the patient's participation in the trial. The electronic patient record will be updated to record participation.

Alongside providing explicit consent to take part in the study, the men will also be asked on the consent form if they are willing to consent to (i) being contacted by a qualitative researcher to undertake an interview and (ii) being contacted about other research. Declining to consent to these will not disqualify a man from participating in the main trial.

All patients who agree to participate in qualitative interviews (verbally determined at initial phone call by the CRN and confirmed in the main trial consent form that they agree to be contacted by the qualitative researcher), will also be asked to provide informed consent at the time of the interview. Written consent will be taken for patients being interviewed in person, and verbal consent (recorded) will be taken for those being interviewed by phone.

The initial expression of interest form includes an option to participate in a brief interview for those who decline to participate in TRIUMPH. Patients who decline participation at the CRN phone call, or when reminded for the return of their baseline questionnaire and consent form, may also be asked if they wish to take part in an interview. Patients who indicate they would like to be interviewed will be contacted by telephone or email to arrange a convenient time and verbal consent will be taken at the time of the interview.

7.2 The randomisation scheme

GP practices will be the unit of allocation to the two study arms. Practices will be randomised on a 1:1 basis to receive either the intervention or continue care as usual (control group) by a BRTC statistician who will be blinded to the identity of practices. This will be done after the practice list searches have been conducted and lists have been screened by GPs. As there are a relatively small number of GP practices in the trial, minimisation will be used to allocate practices to treatment arms to ensure balance. Randomisation will be minimised by centre (Bristol and Southampton), practice size and area-level deprivation (IMD) of the practice.

All men registered at a GP practice randomised to the manualised and standardised care pathway who agree to participate will follow the active management (non-pharmacological "Intervention arm")

and all men registered at a GP practice randomised to the Usual care ("Comparator arm") will receive current NHS standard management.

7.3 Blinding

Two statisticians will support this trial. The senior statistician co-applicant will be blinded throughout the trial. A junior statistician will perform all disaggregated analyses according to a pre-specified statistical analysis plan and will attend closed DMC meetings as required. The CRN support team will be blinded to minimise the selection and recruitment bias. The remaining members of the study team will remain blinded to aggregate data only.

7.4 Baseline data

Clinical data will be collected from patient note review (following written consent). Patient reported data will be collected via patient questionnaire. Validated questionnaires will be used for patient reported outcomes (see section 7.5).

Table 1 Summary of baseline data collection

Clinical	Co-morbidities, relevant prescribed medication (including alpha-blockers etc.).
Laboratory	Urinary analysis and renal function, if available in notes 6 months prior to TRIUMPH consent.
Patient reported	Age, ethnicity, marital status, height, weight, EQ-5D-5L, IPSS, ICIQ-UI-SF, B-IPQ for all patients and a Bladder Diary (intervention only).

7.5 Trial assessments

	Baseline	**3 months**	**6 months**	**9 months**	**12 months**
Bladder diary	●				
CRF	●		●		●
IPSS	●○		●○		●○
ICIQ-UI-SF	●○		●○		●○
B-IPQ	●○		●○		●○
EQ-5D-5L	●○		●○		●○
Case note review					●○

● Intervention arm ○ Control arm

Figure 1 Overview of trial assessments

7.5.1 Intervention

The intervention arm offers manualised and standardised active management according to the symptomatic presentation of the individual patients. The central aspects of the intervention are:

1. The personal delivery by a nurse/healthcare assistant to educate, emphasise positive aspects, and direct the patient to the relevant steps to take personally.

2. The illustrated booklet of written information "Helping you to take control of your waterworks". The literature is in advanced development in line with Information Standards and Department of Health guidance. It builds on literature already available from BAUS, using 8 patient panel meetings on the general approach to delivery and the specifics of the advice needed for each of LUTS. The sections included are:

- Advice on drinks and liquid intake
- Advice on controlling an urgent need to pee (urinate)
- Exercising the muscles between the legs (pelvic floor) to help stop bladder leakage
- Advice on emptying your bladder as completely as possible
- Advice on getting rid of the last drops
- Reducing sleep disturbance caused by needing to pee.

3. To encourage and gauge adherence to the intervention, we will use regular contacts (initial face-to-face appointment, after one week and optional further contacts 4 and 12 weeks later by phone or email according to patient preference). Subsequent routine HCP contact is not planned.

The sections of the booklet are tabbed to allow manualised tailoring by the HCP with discrete stickers. The booklet is water-resistant and able to lie flat when open. Pictures used for clarity will avoid the use of potentially embarrassing images.

The research/practice nurse/healthcare assistant will be provided with a decision tool to assist them in tailoring the treatment for each patient at the baseline visit.

7.5.2 Comparator

Usual care (the comparator arm for TRIUMPH) in this study requests sites to continue to follow their standard local practice for trial patients. The qualitative aspect of this trial will explore what usual care looks like for a sample of comparator and intervention practices.

7.5.3 Trial follow-up

Men will complete self-reported outcome measures (IPSS, ICIQ-UI-SF, EQ-5D-5L and B-IPQ) at 6 and 12 months post enrolment. To encourage on-going participation a newsletter from the study team will

be sent to all participants at 3 and 9 months to remind patients about the study and their involvement. Data extraction of GP records at 12 months (resource use) will be used to gauge use of health care resources (e.g. GP consultations, medications and secondary care referral).

7.6 Qualitative Research

A qualitative component will be included within the study to evaluate patients' attitudes to, and experiences of, non-pharmacological and non-surgical interventions for men with LUTS. Patients within the control group will be included to explore their LUTS experience. HCP views on the interventions will also be explored. In addition, facets of trial participation will be explored. A small group of patients who decline to participate in TRIUMPH will be interviewed to explore their reasons for not participating and identify potential areas of improvement in the trial design.

Semi-structured interviews will be conducted during the pilot phase (control group excluded from this stage). We will conduct qualitative interviews with study participants and clinicians involved in the trial at baseline and following the intervention package. The purpose of these interviews is to explore LUTS generally, the acceptability and attitudes to the proposed interventions and to improve understanding of the outcomes and how they may be implemented into clinical practice. Theoretical purposive sampling will be used to cover the population characteristics.

7.6.1 Objectives in the Intervention arm

a) To explore the perspectives regarding the intervention through patient interviews at baseline (following baseline study visit)

Health-seeking drivers: what treatments have they received and how do they perceive their effectiveness; product usage; treatment preferences – what would they like/expect to be offered?; expectations regarding outcomes; anticipated compliance with the intervention.

b) To explore through patient interviews at follow-up (6-12 months following consent)

Perspective on intervention: positive aspects of the intervention; negative aspects of the intervention; perspectives on compliance/adherence.

c) To explore acceptability of the treatment pathways through patient interviews during feasibility (months 7-10, following baseline study visit)

Willingness to participate in the intervention: acceptability of follow-up pathway; perspectives on standard and intervention pathways; what support is expected to encourage adherence.

7.6.2 Objectives in the Usual care (control) arm

a) To explore perspectives regarding usual care through patient interviews at baseline (following return of baseline questionnaires)

Health-seeking drivers: what treatments they have received and how they perceive their effectiveness; product usage; expectations regarding LUTS.

b) To explore perspectives regarding usual care through patient interviews at follow-up (6-12 months following consent)

LUTS experience since baseline: any treatments received; product usage; expectations for future LUTS care

7.6.3 Objective of staff interviews

a) To explore through HCP interviews (during trial recruitment and follow-up period)

Recruitment process drivers and barriers: randomisation perspectives – cluster design acceptability, presence of preference; usual care/ intervention perspectives; outcome perspectives and perceived compliance – where able for those who have returned and discussed the intervention; retention of participants/loss to follow-up.

7.6.4 Objective of decliner interviews

a) **To explore through interviews with those who declined to participate**

Reasons for non-participation - reasons specific to TRIUMPH, other reasons, discussions with others during decision-making, previous experience of research; approach and information received – how heard about TRIUMPH, information provided, understanding of TRIUMPH aims, trial processes involved in participation (cluster randomisation, equipoise, arms).

7.6.5 Trial Interviews

A standardised approach will be employed to explore the above areas in accordance with published qualitative research methods. Face-to-face patient interviews will be conducted where possible with telephone interviews included for remote study sites. Interviews will be carried out by an experienced qualitative researcher. Interviews will be semi-structured and follow a topic guide (informed by literature review and discussion between study researchers) which will encourage participants to discuss their perspectives with regard to the aims above. Interviews will be audio-recorded, transcribed verbatim and uploaded into a qualitative software package (NVivo10) to aid data management. Analyses will be conducted by the qualitative researcher on an ongoing basis in an iterative manner, according to principles of thematic content analysis (18). Recordings will be listened

to and transcripts read and re-read for familiarisation. Segments of text will be 'coded' by assigning descriptive labels. Codes will be grouped on the basis of shared properties to create themes and coded transcripts will then be examined and compared to inductively refine and delineate themes (constant comparison) (19) (20).

A subset of interviews will be independently analysed by a second study researcher and coding discrepancies discussed to maximise rigour and reliability. Plausibility of data interpretation will be further discussed within the study team throughout the analyses. Descriptive summary accounts of the audio-recordings and interviews will be prepared.

7.6.6 Participant sampling and recruitment

Theoretical purposive (non-probability) sampling will be used to ensure the diverse characteristics of the population are sampled (e.g. participants of differing ages, clinical history, duration of symptoms and at follow-up in the intervention arm, components of the package received and drop-out/ adherence). Geographical distribution will also be factored to ensure representation of varied practice populations (21). Sampling and analyses will continue in iterative cycles until no new themes are emerging and established themes cease evolving (data saturation) (22). It is anticipated approximately fifteen participants will be required for the feasibility stage, followed by a maximum of thirty patient interviews for both baseline and follow-up evaluation in the Intervention arm and fifteen at both time points in the Usual care arm during the main trial. Where possible we will conduct follow-up interviews with the same participants as the baseline interviews to capture reflective perspectives. However, additional participants may also be required to ensure representativeness of the spectrum of interventions delivered and those considered compliant/adherent to the interventions.

A convenience sample of a maximum of twenty HCPs will also be interviewed to capture the variability of the practice populations and both usual care and intervention practices involved.

7.6.7 Interview conduct

A question will be included in the expression of interest form to identify those who wish to take part in interviews despite declining participation in TRIUMPH. Patients who decline participation at the CRN phone call, or when reminded for the return of their baseline questionnaire and consent form, may also be asked if they wish to take part in an interview. A separate PIL will be provided for those who express interest in taking part. Verbal consent will be provided at the time of interview for these interviews.

All trial participants will be asked at the initial screening telephone call if they are willing to be contacted about taking part in a qualitative interview. This question will also be included on the consent form which is returned to the study team to record explicit consent to participate in the main study. Those who indicate that they are willing to be contacted will be provided with a separate PIL for the qualitative study.

Following an opportunity to discuss concerns or questions regarding the qualitative study, the participant will be asked to provide informed consent to take part. Written consent will be taken for patients being interviewed in person, and verbal consent (recorded) will be taken for those being interviewed by phone.. Participants will be informed that non-participation or withdrawal at any time from the qualitative study will not affect their involvement in the main study, or their clinical care.

7.7 Methods to protect against other sources of bias

a) Ensuring standardisation of intervention and outcome measurement (performance bias)

All HCPs involved in delivery of the intervention will receive the same training and will be provided with a flow chart decision tool to assist them with tailoring the appropriate advice to the patients' symptoms. This will be a 2-hour training session undertaken during site set-up, developed by Chief Investigator and senior investigator in each centre (Bristol: Prof Marcus Drake; Southampton: Margaret Macaulay).

b) Loss to follow up (attrition bias)

Loss to follow-up in a previous trial of non-pharmacological treatment for men with urinary incontinence after prostate surgery (23) was 5 to 10% at one year. However, a more conservative estimate of just over 30% 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 (REC) approval. This will include:

- reminders to men via phone/ text/ email/ post. Three contact attempts will be made for reminders post consent, but only one attempt after the CRN screening phone call to obtain baseline questionnaires and completed consent form
- completion of questionnaires over the phone if required
- obtaining alternative contact details
- using vouchers as retention incentives (24)
- contacting their practice to check their contact details on their record are still valid (25)

c) Measurement bias

Measurement bias will be minimised by using validated questionnaires for patient-reported outcomes.

d) Other sources of bias (detection bias)

To prevent cross-contamination if both arms are run in the same site, we propose cluster randomisation of GP practices, so each practice will recruit participants either to the Intervention or the Usual care arm. Accordingly, group allocation cannot be concealed from the man or the staff. However, the screening of patient databases will be undertaken before practice randomisation and practice allocation will be concealed to men until after they consent to participate in the study. Participation in the trial could influence delivery of care in the control arm practices. However, the study population draws on prevalent rather than incident cases, and the low likelihood of contact between GPs and patients in the duration of the study is not considered to be a high risk of detection bias. We will monitor participation rates in both treatment arms. Random allocation minimised on centre, practice size and area-level deprivation will reduce the threat of confounding due to baseline differences between groups. The primary analysis conducted will be adjusted for practice-level characteristics used in randomisation. Sensitivity analyses will be performed by adjusting for other baseline confounders that prove to be imbalanced between the two groups.

All men will be actively followed up, with analysis based on the intention-to-treat principle. All analyses will be clearly predefined in a Statistical Analysis Plan (SAP) to avoid bias.

7.8 Withdrawal criteria

The physician responsible for a patient retains the right to advise withdrawal of a patient from a trial for appropriate medical reasons, be there any individual adverse events or new information gained about a treatment. Participants can withdraw from (a) complying with the allocated trial treatment or (b) providing data to the trial, at any time for any reason without affecting their usual care. In both cases efforts will be made to report the reason for withdrawal as thoroughly as possible in a “Withdrawal/ discontinuation” form.

Should a participant wish to withdraw from receiving the allocated trial treatment, efforts will be made to continue to obtain follow-up data, with the permission of the patient or family as appropriate. Any data collected up to the point of withdrawal will be retained for analysis unless the participant specifically requests otherwise.

7.8.1 Post trial care

Following the end of the trial, patients in the intervention arm will be able to retain the booklet provided, and patients in the control arm will be provided with the booklet if requested. Participants

will be informed of this in the written information given to them when they are considering entering the trial.

8 SAFETY

Serious and other adverse events will be recorded and reported in accordance with the Good Clinical Practice (GCP) guidelines and the Sponsor's Research Related Adverse Event Reporting Policy.

8.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: ● results in death ● is life-threatening ● requires inpatient hospitalisation or prolongation of existing hospitalisation ● results in persistent or significant disability/incapacity ● consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" 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.

8.2 Operational definitions and responsibilities for (S)AEs

Due to the nature of LUTS, AEs are expected to occur throughout the course of the disease, these AEs are expected to be of low risk to the health of the patient. GP practices are responsible for reporting SAEs for their trial participants during the course of the trial. However, participants are also asked to self-report any inpatient stays in their follow up questionnaires, which will prompt a GP note review if an unreported SAE is indicated. The SAE information will then be completed and verified by the GP practice.

The Principle Investigator at each GP practice is responsible for categorising whether SAEs are serious, and expected/related. Expectedness decisions will be guided by the information below; other

factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described below is considered unexpected.

The following events are expected in this patient population:

- Hospital admissions – elective and emergency – that can be explained directly or indirectly by their LUTS
- Urinary Tract Infections (UTIs) related to their LUTS
- Urinary retention

8.3 Recording and reporting of SAEs

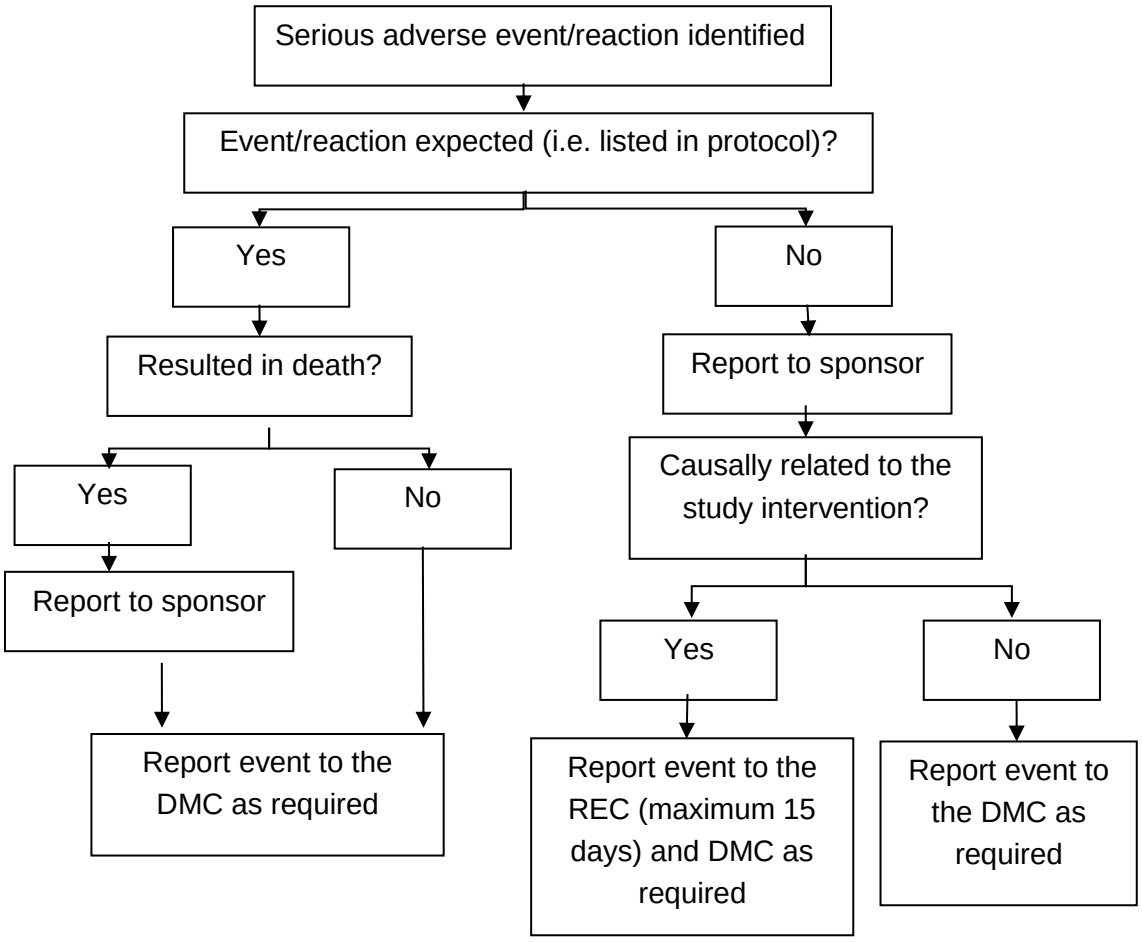
Expected SAEs will NOT be reported to the Sponsor or REC (unless they are fatal) but instead a record of these expected SAEs will be collected and included in summary reports, as agreed by the Data Monitoring Committee (DMC) and will be provided to the DMC.

Unexpected SAEs will be reported to the Sponsor. Unexpected SAEs which are causally related to the intervention will be reported on to the REC.

The definition of hospitalisation is an unplanned overnight stay. Note however that the patient must be formally admitted – waiting in outpatients or ED would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for “social reasons” (e.g. respite care, the fact that there is no-one at home to care for the patient). Also, if patients had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE.

Participants will be monitored for SAEs from the time of consent until the end of their participation in the study, i.e.12 month after enrolment in the trial.

All reportable SAEs must be documented on UHBristol SAE reporting forms and emailed securely to the central research team immediately who notify the Sponsor (or delegate) and REC within 15 days of the centre staff becoming aware.



For each SAE the following information will be collected

- Full details in medical terms and case description;
- Event duration (start and end dates, if applicable);
- Action taken;
- Outcome;
- Seriousness criteria;
- Causality (i.e. relatedness to trial/intervention), in the opinion of the investigator;
- Whether the event would be considered expected or unexpected.

Each SAE must be reported separately and not combined on one SAE form. Any change of condition or other follow-up information relating to a previously reported SAE should be documented on the appropriate SAE follow up form and events will be followed up until the event has resolved or a final outcome has been reached.

All other adverse events not deemed serious will be collected from participant medical records at the end of their 12 month involvement in the trial, as part of the primary and secondary outcomes for the trial.

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

This study is powered to detect a mean change of 2 points on our primary outcome of IPSS scores at 12 months. This difference was chosen because while the recognised minimum important difference in IPSS scores is 3.0 (26), men may be bothered by just one symptom (e.g. nocturia).

To inform the sample size calculation a scoping search was conducted with local practices within NHS Bristol CCG to gain a sense of the likely number of patients available on their lists based on our inclusion and exclusion criteria. This search suggested that an average sized practice might identify 100 patients. Assuming that 50% of these patients will be eligible and 70% consent, each practice would consent 35 eligible patients. Our estimates of eligibility rates, consent and loss-to-follow up are conservative and based on our experience running pragmatic trials.

We estimate that 840 patients are needed from at least 24 practices to detect a difference in IPSS scores of 2 (common standard deviation of 5: in line with the assumptions made in the UPSTREAM study (3)) with 90% power and significance level 5%. Our estimate incorporates a design effect to account for clustering of effects in practices which assumes that practices will be able to recruit 35 patients each and that the intra-class correlation between practices would be 0.05 – an estimate in line with results from other primary care studies (27). We allowed for up to 30% of men being lost to follow-up.

9.2 Planned recruitment rate

Figure 2. Participant recruitment projection *Number of men recruited (y-axis) is plotted against recruitment month (x-axis). Recruitment month 1-4 is the internal pilot phase. Allowance is made for slower recruitment during Christmas and Summer periods***.**

We propose a 12-month recruitment period (months 7 to 18 inclusive) to identify, contact and consent 840 prevalent patients as specified in our sample size estimates. In our recruitment progression estimates (Figure 2) we assumed that recruitment might be slower in the first few months as practices become established and any difficulties are identified and resolved. We also allowed for lower recruitment during the summer and Christmas periods and allowed for a second wave of recruitment from the original patient list to be performed part-way through recruitment should this be necessary.

9.2.1 Internal pilot

The internal pilot is primarily designed to verify that recruitment is possible. We will decide about the feasibility of the trial after 4 months of recruitment. Based on our projections, we expect to have recruited 120 patients by this point (See Table 2 for progression criteria).

The trial would be halted if we are unable to recruit more than 90 participants by the end of month 10, as it would be unlikely that we could recruit our required sample size without a substantial extension. If between 91 and 110 patients are recruited, we will review our recruitment strategy and identify any potential barriers to recruitment and consider the need for recruiting additional sites. In this case we

will consider the trial feasible and will consider only minor changes to the recruitment strategy. During the internal pilot phase, the TMG will meet monthly to review recruitment rates and decide whether further actions can be taken to improve them.

Table 2 Progression Criteria

	1. The number of practices agreeing to take part is at least 18 (75%) by the end of month 6. AND 2. The number of patients recruited is at least 120 by the end of month 4 of the recruitment phase.
	1. The number of practices agreeing to take part is between 12 and 17 (50-74%) by the end of month 6, we will review our recruitment strategy in conjunction with the independent Trial Steering Committee (TSC) and the HTA. OR 2. The number of patients recruited is between 91-110 by the end of month 4 of the recruitment phase.
	1. The number of practices agreeing to take part is less than 50% by the end of month 6 OR 2. The number of patients recruited is less than 90 by the end of month 4 of recruitment phase.
NOTE: Achieving all green targets would almost certainly mean proceeding to the full trial; whereas achieving predominantly red targets would almost certainly indicate that a full-scale RCT is not feasible and the trial would be discontinued	

9.3 Statistical analysis plan

All analyses and reporting will be in line with CONSORT guidelines and its extension for cluster randomised trials. Primary analyses will be conducted on an intention-to-treat (ITT) basis. A full statistical analysis plan will be developed and agreed by the Trial Steering Committee prior to undertaking analyses of the main trial.

9.3.1 Summary of baseline data and flow of participants

Descriptive statistics will be used to summarise characteristics of practices and patients and compare baseline characteristics between groups. Means and standard deviations will be used for continuous and count outcomes or medians and interquartile range if required for skewed data. Categorical

variables will be summarised using frequencies and proportions. Baseline variables to be explored include those described in section 7.4. Patient-reported outcome scores based on standardised questionnaires, including the primary outcome of LUTS score, will be calculated based on the developers' scoring manuals and missing and erroneous items will be handled according to these manuals.

9.3.2. Primary outcome analysis

The primary outcome is IPSS score collected at 12 months post-consent. It will be described in each treatment group using means and standard deviations. Comparisons between treatment arms will be made using a multilevel linear model to allow for clustering within practices adjusting for baseline IPSS scores and practice-level variables used in the randomisation. We will explore whether there is clustering by the nurse/healthcare assistant delivering care (in the Intervention arm) and account for this in our models if present. The underlying assumptions of this model will be checked, and analyses adjusted accordingly.

9.3.3 Secondary outcome analysis

Secondary endpoints in this study are described in section 3.4 and these explore LUTS, measures of quality of life, self-management, adverse events, use of LUTS medication and referrals to primary and secondary care. Continuous outcomes will be studied in the same manner as the primary outcome using multilevel linear models to allow for clustering within practices adjusting for baseline measures of the outcome where available. Binary outcomes will be studied using multilevel logistic regression models allowing for clustering within practices. Count variables will be studied using multilevel Poisson regression models - or negative binomial model depending on the distribution of counts - allowing for clustering within practices. All models will adjust for variables used in the randomisation, the underlying assumptions of the models will be checked, and analyses adjusted accordingly.

9.3.4 Planned further exploratory analyses

We will conduct a small number of further exploratory analyses to study the treatments received in both arms and categories of LUTS that patients present. We will also explore how the EQ-5D-5L responses relate to the IPSS-QoL.

9.3.5 Proposed frequency of analyses

The main analysis will be performed when all 12-month follow up has been completed. An independent DMC will review accumulating safety data at its discretion, but at least annually.

9.4 Subgroup analyses

The effects of the intervention may differ between groups of patients according to the nature of LUTS experienced at baseline. The ratio of the IPSS voiding subscore to the storage subscore (IPSS-V/S ratio) has been used to describe the relative dominance of voiding to storage LUTS (28). Subgroup analyses will be carried out to assess the difference in treatment effect on the primary outcome according to the voiding/storage subscore ratio reported at baseline. Effect modification will be assessed by including an interaction term in the regression model and formal tests of interaction will be performed to test whether the treatment effect differs between these groups.

9.5 Adjusted analysis

All primary analyses will adjust for the outcome as measured at baseline and variables used in the randomisation. Secondary analyses will adjust for any prognostic variables demonstrating marked imbalance at baseline (ascertained using descriptive statistics).

9.6 Procedure(s) to account for missing or spurious data

The primary analyses will be based on the observed data and a sensitivity analysis will be conducted where missing data are imputed using appropriate methods based on patterns of missingness.

Data will be entered promptly, and data validation and cleaning will be carried out throughout the trial. Where spurious data are observed, values will be checked against available records

9.7 Economic evaluation

The trial will include a formal economic evaluation comparing the costs and cost-effectiveness of the intervention from an NHS perspective, from baseline to 12 months follow-up. The cost of the intervention and the use of primary and secondary NHS services by the men in relation to their bothersome LUTS, will be estimated through the collection of resource-use data from general practice records and study designed proformas, and will be valued using routine data and GP practice information.

The values from EQ-5D-5L, administered at baseline, 6 and 12 months, will be transformed into utility scores and individual QALYs will be calculated using the area under the curve approach.

Resource use (e.g. number of GP consultations) will be calculated for each arm. Differences in costs and QALYs between the arms will be evaluated using appropriate regression techniques. For the primary economic analysis, cost-effectiveness will be assessed using the Net Benefit framework over a range of values for the QALY and will include the UK cost-effectiveness thresholds of £20,000 - £30,000.

A secondary economic analysis will examine the difference in costs and IPSS score. If neither arm is dominant (i.e. both cheaper and more effective), then an incremental cost-effectiveness ratio (ICER) will be calculated in relation to the IPSS score. If appropriate, Seemingly Unrelated Regressions (SUR) will be used when constructing the ICER, to account for the potential correlation between costs and the IPSS score.

Uncertainty for these analyses will be addressed using cost-effectiveness acceptability curves and sensitivity analyses.

10 DATA HANDLING

10.1 Data collection tools and source document identification

Clinical outcomes will be assessed by participant-completed questionnaires at baseline (postal), 6 months (telephone, postal or online) and 12 months (telephone, postal or online). Case report forms will be completed at the time of the baseline assessment and treatment phase over 12 weeks (intervention only). Details of patient treatment, adverse events and resource use will be abstracted from the patients' primary care medical records at 12 month follow up. We are using standardised outcome instruments. The components and timing of follow-up measures are shown in Figure 1.

Standardised tools being used:

- EQ-5D-5L
- ICIQ-UI-SF
- IPSS
- B-IPQ

For economic outcomes, study designed proformas will be completed by the research or practice nurse/healthcare assistant to collect the resources used in the intervention.

Self-completed questionnaires, which will include the EQ-5D-5L, will be administered to all men at baseline (postal only), 6 and 12 months (telephone, postal or online).

A central administrative database will be set up by BRTC that prompts the Clinical Trials Unit (CTU) when Patient Questionnaires (PQ) are due.

10.2 Data handling and record keeping

Data will be collected and retained in accordance with the UK Data Protection Act 1998 (this process will be reviewed and updated accordingly with any updates to the guidelines).

10.2.1 Clinical data

- The clinical data will be stored using REDCap. REDCap is a secure, web-based electronic data capture (EDC) system designed for the collection of research data.
- Although the system has been developed by Vanderbilt University, the Department of Population Health Sciences (PHS) (University of Bristol, 'UoB') has set up its own infrastructure to host the REDCap application so that all elements reside within UoB.
- REDCap is used solely for anonymized clinical data linked by a participant ID. Email addresses are usually collected as they are essential for the correct functioning of the survey feature.

- All data recorded that has the potential to identify a participant (i.e. DOB, email address) will be marked as 'identifier'. Whilst the PI and Trial Managers can access all data, data exports for sharing can be anonymized by selecting 'remove identifiers' option in the export process. The data set can then be considered pseudonymised at export and does not need further processing.
- Data are stored in a secured UoB server subject to standard UoB security procedures. The full database is backed up daily. Additionally, changes are logged every hour. A disaster/recovery plan is in place as part of the SLA we have with IT Services.
- A combination of field type validation, data ranges, logic and thorough technical and User Acceptance testing is used to ensure the quality of the data collected via REDCap.
- REDCap supports the whole data lifecycle, including database design, data collection, validation, branching logic, analysis, reporting and storage. In addition, REDCap provides automated export procedures for seamless data downloads to common statistical packages.
- REDCap provides a full audit log cataloguing individual changes with date/time, old value, new value and the identity of the user who made the change.
- REDCap user roles can be used in combination with filed validation as identifier to determine the data that can be viewed by different members of the team. This facility can be used to avoid unblinding the statistician if necessary.
- Data entry can be performed by accessing the REDCap application directly or via surveys. In order to access the application directly, users will be added to the system (following request from the Trial Manager) by the Data Manager. It is the Trial Manager's responsibility to add the user to a specific project and role.
- Data can be collected offline using mobile devices. The data can be uploaded to the main REDCap server once good WIFI connection is available.

10.2.2 Administrative Data System

- The Administrative data will be stored in a central clustered Structured Query Language (SQL) database. The database is backed up daily and uses binary log files. A disaster/recovery plan is in place as part of the SLA we have with IT Services.
- The Administrative system provides a full audit log cataloguing individual changes with date/time, old value, new value and the identity of the user who made the change.
- A combination of field type validation, data ranges, logic and thorough testing is used to ensure the quality of the data collected via the user interface.

- The Administrative system resides behind University of Bristol firewall. All users will be required to have a University of Bristol user account, which means they are a member of staff or have honorary status and bound by University of Bristol policies and rules.
- Access to the Administrative system is by username and password with user rights assigned by a BRTC administrator, at the request of the Trial Manager.

10.2.3 Docmail

Practices are well acquainted with using Docmail for research purposes and prepare the information from their own database systems. Practices will be using Docmail for the purpose of inviting patients to participate in research which they have a right to do in the NHS. The Docmail website uses the highest strength 256 bit RSA encryption, so patient information will be secure.

10.2.4 Bristol Online Survey (BOS)

Patients wishing to complete their expression of interest online will be able to do so via the BOS system. Patients who indicate they are interested in taking part will complete their contact information which will then be uploaded to the administrative system and will then fall under the same restrictions as other personal details (ie. behind the University of Bristol firewall).

10.3 Access to Data

10.3.1 Source data

For monitoring purposes, the PI will allow monitors from the sponsor (or delegate), persons responsible for the audit, representatives of the REC and of the Regulatory Authorities to have direct access to source data/documents.

10.3.2 Anonymised trial data

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

10.4 Archiving

This trial will be sponsored by UoB who will also be the data custodian. All research data will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all paper records will be destroyed by confidential means.

11 TRIAL MANAGEMENT

The trial is supported by the Bristol Randomised Trials Collaboration (BRTC). The BRTC is an UK Clinical Research Collaboration registered Clinical Trials Unit. The trial will conform to the BRTC standard operating procedures. The central research team will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators

11.1 Day-to-day management

The Study Office will be based in the BRTC within Population Health Sciences at the University of Bristol and will provide day to day support for the research sites. The Trial Manager based at the BRTC will take responsibility for the day to day supervision of study activities. As per BRTC's business and costing model the Senior IT manager will oversee all IT aspects of the study, while the Senior Trials Manager will provide mentoring and guidance to the trial manager and advice to the team on generic coordination issues. The TRIUMPH Study Office Team will meet at least every 2 weeks during study start-up phase to ensure smooth running and trouble-shooting.

11.2 Trial Management Group

The trial will be managed by a Trial Management Group (TMG), which will meet face-to-face/by teleconference approximately every 2 months. The TMG will be chaired by a Chief Investigator and will include all members of the named research team (see Co-investigator details).

11.3 Trial Oversight

Serious Adverse events will be documented and reported by the study team in accordance with University of Bristol's Service Level Agreement (SLA) with UH Bristol who manages SAE reporting on behalf of the University. For that reason, all SAEs must be recorded and reported to UH Bristol, in accordance with UH Bristol Research Safety Reporting Standard Operating Procedure. UH Bristol will regularly inform the University about SAEs. Expedited reporting takes place where necessary to agree corrective/Preventative actions.

11.4 Principal Investigator/research or practice nurse

Principal investigators (PIs) and research/practice nurses at each site will be checking for SAEs/AEs when they have contact with participants. They will be responsible for:

- Using medical judgement in assigning seriousness, causality and expectedness.
- Ensuring that all SAEs are documented and reported to the study team on becoming aware of the event and provide further follow-up information as soon as available.
- Maintain regular contact with the TRIUMPH Study Office;
- Contact potential participants by sending them the PIL and EOI form
- Keep a log of whether eligible men are recruited or not (with reasons for non-participation);
- Scan and send paper copies to the Study Office;

- File relevant study documentation (e.g. consent form) in the man's medical records and ensure full and accurate records are maintained in accordance with Good Clinical Practice Guidelines;

For intervention practices undertaking the intervention delivery with their own staff, the following additional activities are expected:

- Conduct the face to face visit including completion of the associated CRF using the web-based TRIUMPH database;
- Conduct follow-up contact with patients by their preferred method;
- Organise and supervise alternative staff to cover any patient visits scheduled in case of holiday or absence.

11.5 Chief Investigator

The chief investigator has overall responsibility for the study and will be responsible for:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all reportable SAEs including expedited reporting of SAEs to the REC within required timelines.
- Central data collection of SAEs and notifying PIs of SAEs that occur within the trial.
- Ensuring safety reports are prepared in collaboration with appropriate members of the TMG group for the main REC and DMC and TSC.

11.6 Sponsor

University of Bristol, as Sponsor, will be responsible for overall oversight of the trial.

11.7 Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial, monitor trial progress and conduct and advise on scientific credibility. The membership will consist of an independent chair (Prof. Peter Bower), together with at least two other independent members, and the trial manager and the Chief Investigator (CI: Mr Marcus Drake) will also attend. The TSC will also comprise of one patient representative. Observers may also attend, as may other members of the Trial Management Group (PMG) or members of other professional bodies at the invitation of the Chair. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy

11.8 Data Monitoring Committee (DMC)

The DMC will also have an independent chair (Mr Chris Harding), and will monitor accumulating trial data during the trial and make recommendations to the TSC as to whether there are any ethical or

safety issues that may necessitate a modification to the protocol or closure of the trial. It is anticipated that both the TSC and the DMC would meet twice a year.

In accordance with the Trial Terms of Reference for the DMC, this group will be responsible for assessing safety and efficacy of the trial.

At the first DMC meeting, the committee will agree on its charter of operations and advise on the way safety data should be presented at future DMCs and whether stopping rules for efficacy or safety are required. The DMC will report findings and recommendations to the TSC.

11.9 Patient Advisory Group (PAG)

We have identified an expert panel of service users who will form the PAG. This group will consist of five men who have volunteered to North Bristol NHS Trust's Research and Innovation Department to advise on research from a user perspective. Patient advice has already been sought about the proposed study and its design and patient facing documents. The PAG will meet biannually in year 1 and 3 and annually in year 2. We also have patient representatives on both our TMG and TSC. We are committed to obtaining the input of service users at every stage, from design to production of plain English summaries for dissemination.

12 MONITORING, AUDIT AND INSPECTION

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the sponsor, the relevant REC and for inspection by other licensing bodies.

All UoB studies that are registered on the Research Governance system will be eligible for monitoring by an independent service provider (an SLA is in place with UH Bristol to provide this).

Compliance with the GCP guidelines for monitoring is often interpreted as requiring intensive site monitoring. However, "the extent and nature of the monitoring should be proportional to the objective, purpose, design, size, complexity, blinding, endpoints and risks of the study." (GCP, section 5.18.3).

The sponsor usually delegates some of the monitoring to the central research team. The following checks would be typical:

- That written informed consent has been properly documented
- that data collected are consistent with adherence to the study protocol
- that CRFs are only being completed by authorised persons
- that SAE recording and reporting procedures are being followed correctly
- that no key data are missing
- that data is valid
- review of recruitment rates, withdrawals and losses to follow up.

On a regular basis we will monitor the percentage of LUTS patients that meet the eligibility criteria and report the percentage of patients who consent. To assess the generalisability of the participants, the characteristics of consenting participants and non-consenting will be compared. We will also report to the DMC if requested, preliminary data on event rates observed in the trial population: infections, GP consultation rates, SAE rates, dropout rates, and transfer to a different treatment (i.e. surgery).

12.1 Protocol compliance

There will be no prospective, planned deviations or waivers to the protocol. Accidental protocol deviations can happen at any time, but they must be adequately documented on the relevant forms and reported to the CI and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

12.2 Notification of Serious Breaches to GCP and/or the protocol

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

a) the safety or physical or mental integrity of the subjects of the trial; or
b) the scientific value of the trial

The sponsor must be notified immediately of any case where the above definition applies during the trial conduct phase. They will assess the seriousness of any breach as per the appropriate SOP.

13 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with:

- Good Clinical Practice (GCP) guidelines
- UK Policy Framework for Health and Social Care Research

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC.

Before any site can enrol patients into the trial, the CI/PI or designee will obtain confirmation of capacity and capability for each site in-line with HRA processes.

For all amendments the CI/PI or designee will confirm with the Sponsor, the HRA (+/- REC) and sites' R&D departments that permissions are ongoing.

13.1 Peer review

The proposal for this trial has been peer-reviewed through the NIHR HTA peer-review process, which includes independent expert and lay reviewers.

13.2 Research Ethics Committee (REC) review and reports

Ethical and Health Research Authority (HRA) approvals will be sought through the HRA for the trial and the qualitative work embedded within the trial. We believe the proposed research does not pose any specific risks to individual participants nor does it raise any untoward ethical issues.

All sites will be expected to confirm capacity and capability by signing the relevant HRA document applicable to their site.

Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by a UK Research Ethics Committee (REC). Any amendments to these documents, after a favourable opinion from the REC/HRA has been given, will be submitted to the REC/HRA for approval prior to implementation.

All correspondence with the REC will be retained in the Trial Master File (TMF)/Investigator Site File (ISF). An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the study and if the study is ended prematurely (including the reasons for the premature termination). Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

GCP training will be carried out by certain staff members depending on their delegated responsibilities within the trial, the level of training required will be determined according to the NIHR Delegation and Training Decision Aid. Informed consent to participate in the trial will be sought and obtained according to GCP guidelines.

13.3 Amendments

The Sponsor will determine whether an amendment is substantial or non-substantial. All amendments will be processed through the HRA and where appropriate the REC. If applicable, other specialist review bodies (e.g. CAG) will be notified about substantial amendments in case the amendment affects their opinion of the study. Amendments will also be notified to NHS R&D departments of participating sites to confirm ongoing capacity and capability to deliver the study.

13.4 Ethical Issues

The main ethical issue is the need to select one of two possible therapy pathways for men with LUTS, based on the randomisation of their practice, which may not be fully in line with the participant's perceived values or preferences. For the purposes of the trial, it will be essential that men are fully informed regarding present knowledge of the process and outcome of the option applicable to their practice. To achieve this, we will design and test participant information literature in collaboration with BAUS before starting the trial, using an expert group composed of patients, clinicians, and lay experts. We will then organise training for participating clinician teams and local research nurses/healthcare assistants.

13.5 Risks and Benefits

There are no risks associated with participation in the trial, other than those routinely associated with standard management of Male LUTS in the NHS. As with all trials the main benefit of participating is an altruistic one to improve care for subsequent men requiring these interventions.

The PIL will provide clear details of the anticipated risks and benefits of taking part in the trial and the study interventions. The risk and benefits of the study will be discussed with the local research nurses as part of the process of providing written informed consent.

NICE guidelines suggest conservative care for this patient population as part of routine care, regardless of whether or not the patient receives this via primary or secondary care. Usual care in this trial is routine clinical practice according to the participant's GP. The TRIUMPH intervention is considered conservative care and therefore, TRIUMPH does not expose any trial participants to treatment outside of what is considered routine care for LUTS. The trial will expose men to the

potential downsides of the established pathways used in clinical practice: those allocated to Usual care may proceed to drug therapy or urological referral without having conservative intervention; while those allocated to personalised, care undergo a therapy phase (12 weeks) which may be considered a delay to definitive management. The overall benefit of participating in the trial is the altruistic outcome of providing high level evidence for future men with LUTS faced with this choice of active management. Clarification of which pathway is cost-effective from a health care and societal perspective will bring benefit in terms of identifying the best approach for future use in the NHS and more widely in other countries.

13.6 Indemnity

The necessary trial insurance is provided by the Sponsor. The PIL provides a statement regarding indemnity for negligent and non-negligent harm.

13.7 Obtaining informed consent from participants

Informed consent will be approached in a proportionate manner according to GCP guidelines. Participants will be given sufficient time to accept or decline involvement and will be free to leave the study at any time. Participants who cannot give informed consent (e.g. due to their mental state) will not be eligible. Participants will be asked to consent to: participation; randomisation; follow up; contact in the future about this and other research; and access to medical records.

All patients in the main trial will be verbally asked via phone if they agree to participate and to be sent the baseline patient pack. A consent form will be included in the baseline patient pack which patients will be expected to sign and send back along with their completed questionnaires; this will confirm their willingness to participate in the study. Patients will be asked how they would prefer to be contacted during the follow-up phase of the trial (phone, post, email).

13.8 Retention of data

To comply with the 5th Principle of the Data Protection Act 1998 (this process will be reviewed and updated accordingly with any updates to the guidelines), personal data will not be kept for longer than is required for the purpose for which it has been acquired. Data will be held in compliance with the sponsor's standard operating procedures. It is intended to follow up the whole cohort of men for at least 5 years, subject to additional funding, and therefore research data will be retained for at least 5 years after close of the study. Documents will be reviewed by the CI before being destroyed.

13.9 Data protection and patient confidentiality

The University of Bristol will be the data custodian. All data held in Bristol will conform to UoB's Data Security Policy and in Compliance with the Data Protection Act 1998 (or equivalent guidance when applicable).

Case report forms at study centres will be completed using the secure web-based TRIUMPH database. Questionnaires from participants will be identifiable only by participant study number and will be returned by the patient by post or via electronic means to the TRIUMPH study team. Any paper copies will be stored in a secure locked cabinet in a locked room.

Data obtained by paper will also be entered onto and maintained on an SQL Server database system maintained by UoB Information Services. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to TRIUMPH study staff. Information capable of identifying participants will not be removed from UoB or clinical centres or made available in any form to those outside the study.

Data sources will be stored for 5 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.

Interviews and recruitment appointments will be recorded on an encrypted digital recorder which will be locked in a secured cabinet at the Department of Population Health Sciences. Recordings will be transferred onto a computer as soon as possible after each interview and stored only in a password protected drive maintained by the UoB. Only the qualitative researchers working on this study will have access to this drive.

Recordings and transcriptions will be named with a study-assigned participant number, centre initials, and the date of recording. There will be no participant identifiers in files, databases, or transcripts, which will only be labelled with study assigned participant numbers. Coding keys matching the name of the participants with their study participation number will be stored in a password protected spreadsheet, which will be maintained and only accessed by the qualitative researchers. All recordings will be coded and securely transferred to a University of Bristol approved transcription company or transcriber that has signed the required confidentiality agreements. All transcripts will be anonymised upon receipt.

All electronic data files will be saved in a secured computer and to a password protected University of Bristol network space, in accordance with the University of Bristol's data security policies.

All nonessential data will be wiped within 1 year of study completion. This allows the study team to contact patients who participated in the study, to receive a plain English summary of the results. Essential documents will be kept for up to 5 years, after which they will be deleted, and all copies destroyed in accordance with the UoB's secure erasure of data policy.

The anonymised interview data (transcripts only) will be uploaded to a 'controlled access' data repository, subject to individual informed consent from the participants. This has been fully explained in the information sheet.

13.10 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The research team and all PIs must disclose any ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

13.11 Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with UoB policy. Data will be kept anonymous on secure access computers. Requests for access to data must be via a written confidentiality and data sharing agreements (DSA) with the CI (or his appointed nominee). Requests for data release outside of the planned analyses should be considered by the TSC.

The DSA should cover limitations of use, transfer to 3rd parties, data storage and acknowledgements. The person applying for use of the data will be scrutinized for appropriate eligibility by members of the research team. All requests will require their own separate REC approval prior to data being released.

14 DISSEMINATION POLICY

A comprehensive plan for disseminating TRIUMPH results will be developed by TMG which will include PPI co-applicants.

The results of the study will be published in the academic press and all participants will be offered a lay summary of the main findings of the study. It is anticipated that the Protocol will be submitted to a prestigious journal, with a view to subsequent publication of the main research output paper. The trial will also be presented at national and international conferences such as the International Continence Society (ICS). This will in turn be used by the national and international community to inform practice, with incorporation into NICE Guidelines and other international guidelines such as those of the EAU.

The findings of the trial will be disseminated nationally through BAUS, as this is the specialist body with the responsibility for guiding clinical practice, policy matters, research priorities, governance and training in matters related to LUTS and benign prostate enlargement (BPE). BAUS is well placed to implement the findings by informing NHS policy (NICE) and by dissemination of evidence-based clinical practice to its members. Our patient panel identified the need for effective dissemination of findings to primary care, and this will be achieved nationally through the Primary Care Urology Society (chaired by co-applicant, Dr Rees). In addition, the host NHS organisation policy on Knowledge Mobilisation is an established route connecting academic output to decision makers for public policy and professional practice.

On completion of the trial a final report will be prepared for the Funder (NHR HTA) and once approved made publicly available on their website.

Study progress and results will be disseminated through the existing communication channels of the BAUS, which has an active twitter account with several thousand followers, respectively. A TRIUMPH Twitter account will be set up to keep interested patients, carers, clinicians, managers and policy makers up-to-date with trial progress.

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