Cardiff University Centre for Trials Research
Canolfan Ymchwil Treialon

The Newcastle Upon Tyne Hospitals NHS Foundation Trust

University of Birmingham

UKCRC Registered Clinical Trials Units

PRIMUS

Primary care **M**anagement of lower **U**rinary tract **S**ymptoms in men:

Development and validation of a diagnostic and decision-making aid.

The PriMUS Study

Protocol Version 2.0 11.09.2017

Sponsor:	**Cardiff University**
Sponsor ref:	**SPON 1553-16**
Funder:	**NIHR Health Technology Assessment**
Funder ref:	**15-40-05**
REC ref:	**17/WA/0155**
IRAS number:	**223941**
ISRCTN number:	**TBC**
Q-Pulse Document Template Number:	**TPL/003/2**

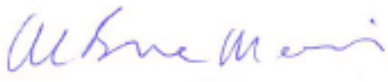
NHS National Institute for Health Research

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant study regulations, GCP guidelines, and Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Director: **Professor Monica Busse**		
Name	**Signature**	**Date**
Professor Monica Busse		**11.09.2017**
Chief Investigator: **Professor Adrian Edwards**		
Name	**Signature**	**Date**
Professor Adrian Edwards		**11.09.2017**
Co-Chief Investigator: **Mr Chris Harding**		
Name	**Signature**	**Date**
Mr Chris Harding		**11.09.2017**

General Information This protocol describes the PriMUS study, and provides information about the procedures for entering participants into the study. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study. Problems relating to the study should be referred, in the first instance, to CTR.

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Study Co-ordination:

The PriMUS study is being coordinated by South East Wales Trials Unit (SEWTU), a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit which is part of the Cardiff University Centre for Trials Research (CTR).

This protocol has been developed by the PriMUS Study Management Group (SMG).

For **all queries** please contact the PriMUS team through the main study email address. Any clinical queries will be directed through the Study Manager to either the Chief Investigator(s) or Co-Investigators.

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Clinical queries:

For clinical queries please contact: **PRIMUS@cardiff.ac.uk** **All clinical queries will be directed to the most appropriate clinical person.**

Serious Adverse Events:

SAE reporting **Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to the PRIMUS Study Team within 24 hours of becoming aware of the event (See Section 15 for more details).** **Contact details:** **Email Address: PRIMUS@Cardiff.ac.uk** **SAE Fax number: 0203 107 0840**

Table of Contents

Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
AUC	Area Under Curve
BCI	Bladder Contractility Index
BOO	Bladder Outlet Obstruction
BOOI	Bladder Outlet Obstruction Index
CI	Chief Investigator
CF	Consent Form
CRF	Case Report Form
CPRD	Clinical Practice Research Datalink
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DO	Detrusor Overactivity
DRE	Digital Rectal Examination
DU	Detrusor Underactivity
EPV	Event Per Variable
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GP	General Practitioner
HB	Health Board
HE	Health Economics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH	International Conference on Harmonization
ICIQ	International Consultation on Incontinence Modular Questionnaire
ICS	International Continence Society
IPSS	International Prostate Symptom Score
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LUT	Lower Urinary Tract
LUTS	Lower Urinary Tract Symptoms
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPSA	National Participant Safety Agency
PCT	Primary Care Trust
$P_{det.Qmax}$	Detrusor pressure at maximum urinary flow
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
PSA	Prostate Specific Antigen
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QL (QoL)	Quality of Life
Q_{max}	Maximum Urinary Flow Rate
R&D	Research and Development
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
ROC	Receiver Operator Characteristic
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SMG	Study Management Group

SSC	Study Steering Committee
TMF	Trial Master File
UTI	Urinary Tract Infection
V_{void}	Volume voided during micturition

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. *(specify substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
Substantial Amendment No.1	V2.0	12.09.2017	•Tightening up of screening and consent process (mandating three index tests in GP screening visit to ensure eligibility of patients) •Addition of patient facing materials •Amendments to patient facing material based on PPI feedback •Amendment and clarification to the wording in the exclusion criteria, including exclusion of men with any contraindications to urodynamics. •Additional safety time-point (RN call to patient 3 days following the urodynamic procedure) •Addition of IPSS questionnaire •Amended definition of adverse events, to only collect those adverse events related to the study •Amended training requirements for nurses

2 Synopsis

Short title	Primary care Management of lower Urinary tract Symptoms in men: Development and validation of a diagnostic and decision-making aid.
Acronym	PriMUS
Internal ref. no.	388
Funder and ref.	NIHR Health Technology Assessment (HTA) 15/40/05
Study design	Diagnostic Accuracy Study
Study setting	Primary Care and the Community
Study participants	Men consulting their GP with Lower Urinary Tract Symptoms (LUTS)
Planned sample size	880
Inclusion criteria	• Men aged 16 years and over. • Men who present to their GP with a complaint of one or more bothersome lower urinary tract symptoms (LUTS)[#] • Men able and willing to give informed consent for participation in study • Men able and willing to undergo all index tests and reference test, and complete study documentation. [#] This would include men on current treatment, but who are still symptomatic
Exclusion criteria	• Men with neurological disease or injury affecting lower urinary tract function • Men with LUTS considered secondary to current or past invasive treatment or radiotherapy for pelvic disease • Men with other contraindications to urodynamics e.g. Heart valve or joint replacement surgery within the last 3 months, immunocompromised/immunosuppressed. • Men with indwelling urinary catheters or who carry out intermittent self-catheterisation • Men whose initial assessment suggests that clinical findings are suggestive of possible: o prostate or bladder cancer* o recurrent or persistent symptomatic UTI** o renal impairment o retention • Men unable to consent in English or Welsh where a suitable translator is not available. This is a multi-centre study based in primary care, and we cannot guarantee translation facilities at all sites *According to standard NHS cancer pathways. If later deemed unlikely, then eligible for study participation. **If UTI successfully treated but LUTS remain, then eligible for study.

Recruitment duration	24 months
Follow-up duration	6 months
Planned study period	1st May 2017 – 30th April 2020
Primary objective	• Develop a statistical model to predict the likelihood of three urological conditions (bladder outlet obstruction, detrusor overactivity, detrusor underactivity) based on a series of non-invasive index tests, with invasive urodynamics as the gold standard • Measure the diagnostic accuracy of the above statistical model in an independent validation cohort.
Secondary objectives	• Develop a series of patient management recommendations and thresholds for clinically useful diagnostic prediction by expert consensus and with reference to current clinical guidelines that map to the diagnoses predicted by the statistical model. • Combine the statistical model and management recommendations into a prototype online tool that will form the prototype decision aid. • Complete a qualitative study to explore the feasibility of introducing the decision aid into primary care including potential acceptability to primary care staff and patients. • Ascertain the number of men in the study referred by GPs to secondary care having considered index and reference test results provided by the study and compare this with 5-year data from the CPRD to estimate potential impact of the aid on referral rates. • Collect NHS costs involved in delivering the new pathway and compare with cost of standard pathway calculated from NHS and other sources.
Primary outcomes	• Sensitivity and specificity of the PriMUS clinical decision aid in diagnosing detrusor underactivity, bladder outlet obstruction and detrusor over activity, in men with lower urinary tract symptoms presenting to primary care. Other measures of diagnostic accuracy which will be measured include positive and negative predictive values and likelihood ratios. All measures will be presented alongside the prevalence of each diagnosis experienced in the study.
Secondary outcomes	• Construction of a patient management algorithm to guide initial treatment for men with LUTS • Construction of a prototype online decision aid for use in primary care • Qualitative analysis of patients and clinicians views on the use of a LUTS decision aid in the primary care setting • Estimate percentage change in referral rates to secondary care for men with LUTS • Estimation of costs / savings of implementation of the primary care LUTS decision aid both from a population and individual patient perspective

3 Study Summary & Schema

3.1 Study lay summary

More than 10% of older men experience the need to pass urine more frequently than usual and often find their sleep interrupted by having to go to the toilet during the night. Some will find that their urine flow rate has become slower, and some will experience loss of bladder control. These problems are grouped into what we call Lower Urinary Tract Symptoms (LUTS). Such problems are distressing for men, affect their work, family and social life, and are a common reason why men visit a general practitioner (GP) with over 60,000 attendances yearly across the UK. They firstly need reassurance that they are not suffering from cancer or any other sinister medical condition. GPs follow established procedures when considering signs of cancer or these more serious conditions, but they have no easily available assessment tools to identify other more common causes of lower urinary tract symptoms (LUTS), or to advise men about the best treatment options for symptom relief. Because of this, men have to be referred to hospital based urology specialists for tests and diagnosis.

The aim of the main PriMUS study is to create a 'decision aid' to help GPs find out the most likely cause of patients' urinary symptoms. The GP will then use the decision aid so that they and the patient can choose the best treatment option together. We believe that this will have many benefits such as getting to the right treatment sooner, avoiding unnecessary hospital visits, and getting those who need to be treated by a specialist there more quickly.

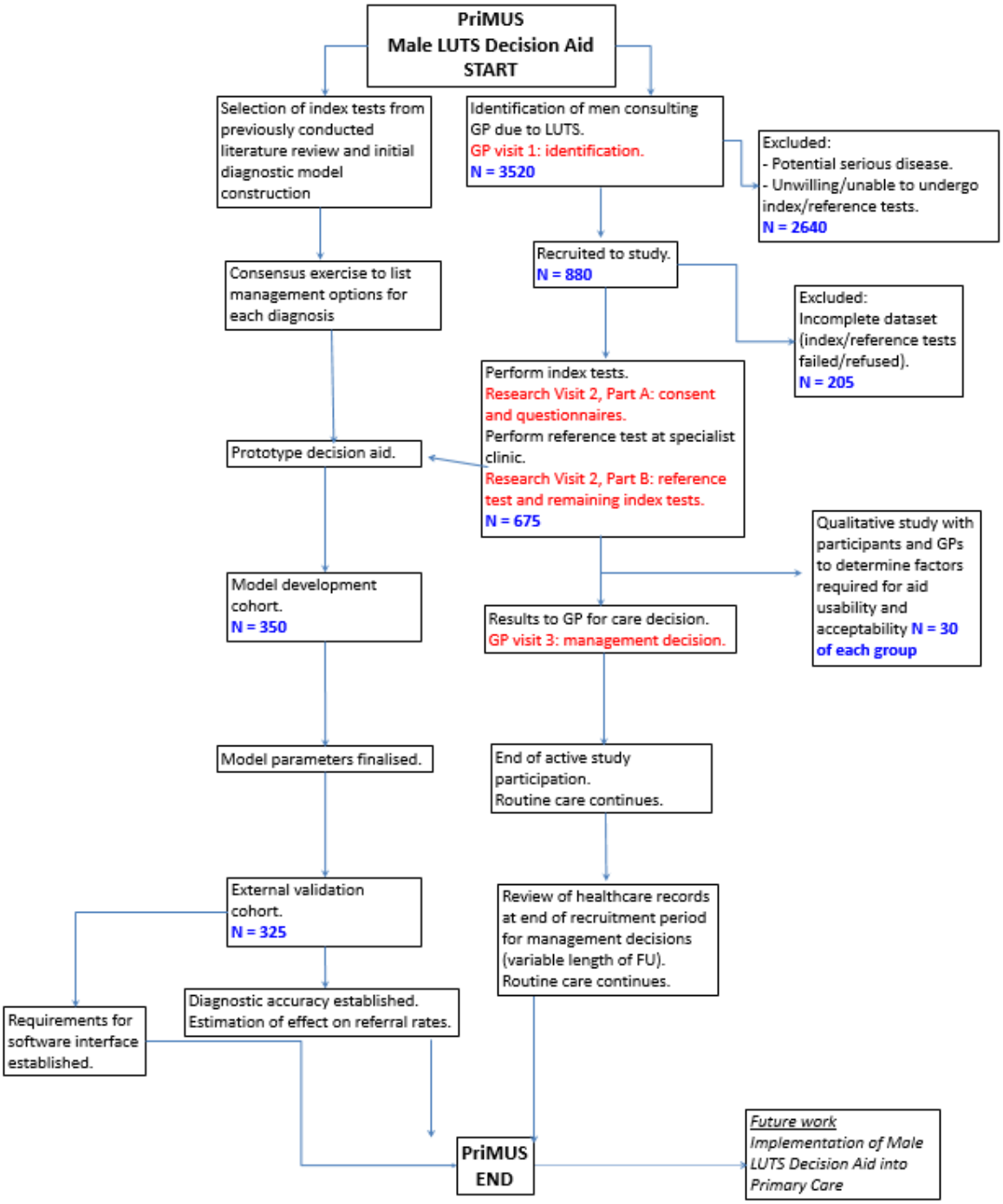
We aim to develop a practical and accurate decision aid for use by GPs to diagnose the cause of LUTS in men and to guide decisions in determining appropriate person-centred treatment. Success of the study will benefit men with LUTS, general practice and the wider health system by:

- Enabling the use of an innovative and proven GP decision making aid across the NHS
- Reducing waiting times before men are assessed and diagnosed
- Giving men early access to appropriate treatment plans personalised to them
- Reducing the number of men needing referral to hospital based urology specialists
- Early referral of those men with more complex problems to specialist urology services

The PriMUS study will demonstrate if a set of simple test results can be incorporated into a computer software programme for use by GPs to establish a diagnosis of the cause of LUTS in an individual and therefore guide selection of appropriate treatment options to relieve symptoms. With the help of general practices across the UK, we will recruit 880 men with LUTS into the study. The tests will include men keeping a diary for a few days to record the timing and amount of urine passed, measuring urine

flow with a small portable machine, and by asking men to complete symptom questionnaires. To assess the performance and accuracy of the tests, all men in the study will also need to have a more complicated test done by a specially trained nurse. This test is called urodynamics and involves the passing of a thin tube into the bladder through which the bladder is then filled with water. Bladder pressure measurements taken during the test may show up problems that might be causing the symptoms. A thin tube is also placed into the rectum and is needed to control for changes in abdominal pressure. By comparing results of the simple tests with results of urodynamics we will identify which simple tests give best prediction of the urodynamic result. The top performing simple tests will then be incorporated into the development of the clinical decision aid so that GPs can manage patients without needing invasive urodynamics. The decision aid will be presented to GPs in a format that allows them to enter test results and then get a readout of the diagnosis and recommended treatment. The study will also consider practicalities for both patients and clinical staff in doing the simple tests in the general practice setting, and the ease in which the decision making tool can be used.

3.2 Study Schema



4 Background

The syndrome of lower urinary tract symptoms (LUTS) occurs mostly in older men and is a bothersome condition detrimental to quality of life (QoL). It can usually be managed without invasive treatment and is very rarely a threat to life or long term health. Male LUTS accounts for four presentations each month in an average sized GP practice (CPRD, 2014). This rate of presentation makes it difficult for GPs to gain sufficient expertise to be confident about diagnosis and management. Consequently, men are frequently referred to urology specialists who often recommend treatments that could have been initiated in primary care. Clinical uncertainty also leads to variation in referral patterns between individual GPs, practices and localities. To address this, the National Institute for Health and Care Excellence (NICE) issued guidance for Male LUTS in 2010 (revised 2015) mapping out initial assessment and conservative management within primary care [1]. Despite this the proportion of men referred to urology services following an incident presentation of LUTS rose from 10% in 2009 to 30% in 2013 (CPRD 2014) at an approximate extra cost to NHS England of £2 million. Implementation projects commissioned by the NHS concluded that further support with access to simple accurate tests, diagnostic protocols and decision aids was needed to facilitate patient management in primary care and ensure best value for patients and the NHS from specialist referral [2].

One of the difficulties faced in primary care is obtaining and interpreting simple clinical measurements that differentiate causes of male LUTS and hence guide effective symptom management. The underlying conditions that disturb lower urinary tract function, with their approximate prevalence are: detrusor overactivity (57%), bladder outlet obstruction (31%), and detrusor underactivity (16%). The diagnoses may appear individually or in combination. An additional contribution to male LUTS arises from ageing-related changes in fluid homeostasis which commonly result in nocturnal polyuria (30%) diagnosed from a 24-hour record of urine output. Nocturnal polyuria, although not a urodynamic abnormality, must be considered when making a diagnosis in men with nocturia as a prominent symptom. About a third of men with LUTS have a combination of two or more underlying causes [3, 4].

There is a need to determine whether performing simple clinical measurements in primary care and combining the results in a statistical model can provide an accurate urodynamic diagnosis for individual patients, which can be used to guide GPs in deciding the best management options. In selecting the component index tests we considered data from the systematic review included in NICE guidance (search date 2009) and updated by ourselves (October 2015). This identified several simple investigations as having potential value in diagnosing the cause of LUTS. The review also identified urodynamics (also known as filling and voiding cystometry) as the reference standard against which

the combination of index tests that provide the best diagnostic accuracy for detrusor overactivity during filling and either bladder outlet obstruction or detrusor underactivity during voiding should be assessed.

In this study, we propose to gather the results of simple clinical tests in primary care and provide a simple statistical decision aid for GPs where the results would be automatically synthesised and diagnostic prediction made. Associated with this prediction, guidance would be given as to which symptom management options are most likely to be of benefit the individual patients. This predicted diagnosis and management options suggested by the aid will then facilitate initial treatment discussions with the patient. Our study is designed to determine whether it is possible to construct a diagnostically accurate decision aid using data provided by the appropriate patient group in the required setting of primary care. In parallel we will assess feasibility and potential benefits of using the aid with referral rate as an important outcome of interest.

4.1 Rationale for current study

Why is the research important in terms of improving the health of the public and/or to patients and the NHS?

Male LUTS is rarely a threat to life or health but patients often find the problem very intrusive to work and social life. The current concentration of diagnostic assessment and initiation of treatment in secondary care usually means a delay in addressing the problem, and inconvenience and extra embarrassment at having to have hospital assessment at a distance from home. A primary care- based decision aid with defined accuracy would firstly mean that the men could undergo the necessary simple tests straightaway organised through the GP surgery and secondly would get a much timelier result regarding predicted diagnosis and choice of management options that are most likely to be effective. For GPs the aid would allay uncertainty around both diagnosis and best management. Specialist urology units would concentrate more on specialist investigation and treating the 10-20% of men who require complex management such as surgery. Those men still requiring early referral or who have not benefitted from simple management options would be referred with a much more informed perspective of their problem with all the initial diagnostics completed making planning of further care quicker and seamless. Reducing rates of referral to secondary care for a number of clinical conditions has been identified as one way of improving delivery of NHS care. Full economic evaluation is not included in this study since the design concentrates on diagnostic accuracy. However, using the rate of consultation and referral documented in the CPRD, we estimate that, if referrals to secondary

care were halved, the NHS in England would be saved about £1.3 million per year from reduced out-patient attendance. Although such a change would require one extra 15-minute consultation with the GP, the relatively low prevalence of the condition means this should not noticeably impact on GP workload. Assessment and initial treatment costs would be unchanged but will be incurred in the primary rather than secondary care setting. Outcome from the patient perspective should not change since GPs will now be receiving the same treatment recommendation from the decision aid that they would have previously been sent from the secondary care urology clinic.

4.2 Health Technologies being assessed

The diagnostic tool/management decision aid will be designed using statistical models that combine variables describing results of the index tests: age, physical examination of the lower abdomen including digital rectal examination (DRE) of the prostate, symptom score from questionnaire, micturition frequency and volume from a voiding diary, urine flow rate and voided volume and post void residual urine volume, to accurately predict the urodynamic diagnosis separately defined by the reference standard of urodynamics. The index tests are all in routine use for this condition within either primary or secondary NHS care and do not involve any physical risk to participants.

Urodynamics, the reference test, is routinely performed in secondary care and involves measurement of bladder pressure during bladder filling and whilst passing urine (voiding) by a thin catheter passed through the urethra into the bladder and rectum. It gives diagnoses of detrusor overactivity during filling and bladder outlet obstruction or detrusor underactivity during voiding. If the test shows none of these diagnoses, then the result is 'normal urodynamics'. The test involves mild to moderate discomfort and risks causing urinary tract infection which occurs in 5% of subjects [5].

5 Study Aims and Objectives

The PriMUS study aims to develop a diagnostic prediction model based on the results of simple clinical tests that can provide a clinically useful prediction of urodynamic diagnosis and to assess the diagnostic accuracy of the model for each of the diagnoses. We will use early clinical management and outcome data to provide an estimate of the likely effect of using the model on rates of referral to secondary care.

5.1 Primary objectives

- Develop a statistical model to predict the likelihood of three urological conditions (bladder outlet obstruction, detrusor overactivity, detrusor underactivity) based on a series of non-invasive index tests, with invasive urodynamics as the gold standard.
- Measure the diagnostic accuracy of the above statistical model in an independent validation cohort.

5.2 Secondary objectives

- Develop a series of patient management recommendations and thresholds for clinically useful diagnostic prediction by expert consensus and with reference to current clinical guidelines that map to the diagnoses predicted by the statistical model.
- Combine the statistical model and management recommendations into a prototype online tool that will form the prototype decision aid.
- Complete a qualitative study to explore the feasibility of introducing the decision aid into primary care including potential acceptability to primary care staff and patients.
- Ascertain the number of men in the study referred by GPs to secondary care having considered index and reference test results provided by the study and compare this with 5-year data from the CPRD to estimate potential impact of the aid on referral rates.
- Collect NHS costs involved in delivering the new pathway and compare with cost of standard pathway calculated from NHS and other sources.

5.3 Primary outcomes measure

- Sensitivity and specificity of the diagnoses of detrusor overactivity, bladder outlet obstruction and detrusor underactivity estimated by the decision aid (using invasive urodynamics as the gold standard reference test)

5.4 Secondary Outcome Measures

- Construction of a patient management algorithm to guide initial treatment for men with LUTS
- Construction of a prototype online decision aid for use in primary care
- Qualitative analysis of patients and clinicians views on the use of a LUTS decision aid in the primary care setting
- Percentage change in referral rates to secondary care for men with LUTS

- Estimation of costs / savings of implementation of the primary care LUTS decision aid both from a population and individual patient perspective.

6 Study Design and Setting

6.1 Design

We plan a prospective diagnostic accuracy study to determine which of a number of simple clinical variables (index tests) collected in primary care and used individually or in combination best predict urodynamic diagnosis in men who present to their GP with lower urinary tract symptoms (LUTS). Two cohorts of participants will undergo the series of simple index tests and the invasive reference test (urodynamics) in community settings. We aim to recruit 880 men from primary care to the study.

The study will follow the NICE pathway for LUTS as standard (http://www.nice.org.uk/guidance/cg97) [1]. Study participants will undergo standard assessment recommended for primary care by NICE. In addition, urine flow rate and residual urine estimation (optional in the NICE pathway and not routine in primary care) will be included. All men in the study will undergo urodynamics as the reference test for diagnostic accuracy; this is a specialist test in the NICE pathway. All results will be given to the GP with the likely diagnosis and recommended management options to decide on further care.

Test variables collected from the first cohort will be used to develop a statistical model which will combine results from the index tests to best predict urodynamic diagnosis from the reference test. The diagnostic accuracy of the model will then be ascertained using the results from the second cohort. A qualitative study will explore the feasibility of creating and introducing a decision aid based on the statistical model for use in primary care, including potential acceptability to primary care staff and patients.

6.2 Setting

Patient screening, invitation, recruitment and consent together with collection of index test variables will take place in Primary Care. We plan that the reference test will take place in GP surgeries and/or secondary clinics within each Research Network hub, using portable equipment and performed by suitably qualified specialist research staff (e.g. Research Nurses).

The qualitative study and field-testing of the prototype decision aid will take place in volunteer GP practices identified from those participating in the main study.

7 Site and Investigator selection

We intend to recruit 100 Primary Care practices across the UK. These will be managed through three study hubs. The networks with whom we have outline agreement to facilitate the study are; Wales Primary Care ('PiCRIS') Research Network; North East England and North Cumbria Research Network and Western Research Network. We may approach other Research Networks across the UK if required.

All GP sites who are interested in participating in the study will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the study. This will be facilitated by each local research network hub.

Before any Site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the PriMUS Study email account (see contact details on page 4):

- The approval letter from the site's R&D Department, following submission of the Site Specific Information (SSI) form
- A signed Study Agreement
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
- A copy of the most recent approved GP letter on host care organisation headed paper

Upon receipt of all the above documents, the Study Manager will send written confirmation to the Principal Investigator/lead Researcher detailing that the site is now ready to recruit participants into the study. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive a study pack holding all the documents required to recruit into the study.

Occasionally during the study, amendments may be made to the study documentation listed above. The Cardiff University Centre for Trials Research (CTR) will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by launch meeting or by teleconference if attendance of key personnel is unfeasible.

8 Participant Selection

Adult (≥16 years) men who consult with their GP with one or more bothersome Lower Urinary Tract Symptoms (LUTS).

Participants are eligible for the study if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Study Manager or local Network Researcher before registration.

8.1 Inclusion /Exclusion criteria

Inclusion Criteria	Exclusion criteria
• Men aged 16 years and over. • Men who present to their GP with a complaint of one or more bothersome lower urinary tract symptoms[#] • Men able and willing to give informed consent for participation in study • Men able and willing to undergo all index tests and reference test, and complete study documentation. [#] This would include men on current treatment, but who are still symptomatic	• Men with neurological disease or injury affecting lower urinary tract function • Men with LUTS considered secondary to current or past invasive treatment or radiotherapy for pelvic disease Men with other contraindications to urodynamics e.g. Heart valve or joint replacement surgery within the last 3 months, immunocompromised/immunosuppressed. • Men with indwelling urinary catheters or who carry out intermittent self-catheterisation • Men whose initial assessment suggests that clinical findings are suggestive of possible: o prostate or bladder cancer* o recurrent or persistent symptomatic UTI** o renal impairment o retention • Men unable to consent in English or Welsh where a suitable translator is not available. This is a multi-centre study based in primary care, and we cannot guarantee translation facilities at all sites *According to standard NHS cancer pathways. If later deemed unlikely, then eligible for study participation. **If UTI successfully treated but LUTS remain, then eligible for study.
	[>]This is a multi-centre study based in primary care, and we cannot guarantee translation facilities at all sites.

9 Recruitment, Screening and Registration

9.1 Participant identification

Potential participants will be recruited from primary care practices across the three network hubs. Recruitment strategies may differ between hubs depending on local geographic and organisational factors.

Participating practices will conduct a search of their patient electronic records using 'pre-defined read codes' to identify all potentially eligible patients who have presented within the last 6 month(s) at the start of the study and at least three additional times throughout the duration of the study. These patients will be 'flagged' in their general practice clinical record using pre-specified read codes in order to allow easy identification of patients, when they contact the surgery, who could be eligible to participate.

Practices will have the option to send relevant patients a letter informing them about the study (on practice headed paper) and a Patient Information Summary Leaflet, and invite the patient to attend the practice for a consultation.

Study posters, leaflets and adverts using electronic visual aids (where appropriate) will be used in practice waiting areas to inform patients about the study.

Participating clinicians will also be asked to approach eligible patients opportunistically during routine practice sessions.

Upon presentation, the PriMUS study will be introduced and the patient information pack (including the Patient Information Sheet, Patient Information Summary Leaflet, Consent Form, Urodynamics Leaflet and Frequency Volume Chart) provided to the patient during their primary care consultation for a complaint of lower urinary tract symptoms.

The GP will have the option to consent a patient to enter the study during the initial consultation visit, if the patient meets the eligibility criteria and they feel this is appropriate. If the patient is not consented during the initial GP Consultation, those who express interest will complete the Consent to Contact Form, which will be passed to the local research nurse. The patient will be contacted by telephone ideally within a week by a research nurse based at the local research network hub, and invited to attend a study appointment.

The GP will complete the Digital Rectal Examination (DRE), Prostate Specific Antigen (PSA) Test and the Physical Examination, (as outlined in NICE clinical guideline CG97) and complete the eligibility checklist, confirming the patient is eligible to enter the study. The GP will also be required to record the results from these tests on a separate eligibility results form. At the study visit with the research nurse, the study will be explained in more detail and the research nurse will establish whether or not the patient wishes to take part. Those who are happy to enter and are eligible will be asked to provide informed consent.

During this appointment, the patient will complete the ICIQ Male LUTS symptom questionnaire and the IPSS questionnaire. The research nurse will complete the patient registration CRF, which will include data collection for the remaining study index tests (i.e. medical history and demographics).

If possible, the research nurse will arrange for the participant to undergo the reference test of (urodynamics) at the same study visit to minimise patient burden, however, in some circumstances this may take place as two separate study visits. This will preferably be performed by the research nurse at the GP practice but with access to the local urology service if required. In some circumstances the urodynamics may take place in a secondary care setting.

9.2 Screening logs

A screening log of all ineligible and eligible but not consented/not approached will be kept at each site to inform adjustment of recruitment strategies and study processes. The logs will also be used to assess any selection bias prejudicing generalisability of the decision aid. When at site, logs may contain identifiable information but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to the study specific email address (PriMUS@cardiff.ac.uk) every month (see section 24 for further detail on data monitoring/quality assurance).

9.3 Informed consent

Eligible patients will be given as much time as they need after the initial invitation to participate before being asked to sign the consent form. GPs will have the option to consent a patient during the initial consultation visit, if the patient meets the criteria and the GP feels this is appropriate. Patients will be notified that they can withdraw consent for their participation in the study at any time during the study period. Patients will also be informed that they have the right to refuse entry to the study without giving a reason and that this will not affect their care in any way.

Informed consent from patients will be sought by suitably qualified, experienced and trained personnel in accordance with the GCP directive on taking consent and before any study related procedures are undertaken.

Patients will be asked to sign a consent form. One copy will be given to the patient, one copy kept in the Site File and a copy send to the CTR. A further scanned copy will be kept in the patient's record.

Only when written informed consent has been obtained from the patient and they have been enrolled into the study can they be considered a study participant. Once consented, participants will be allocated a unique study number (participant ID), which will be the primary identifier for all participants in the study.

The participant will remain free to withdraw at any time from the protocol without giving reasons and without prejudicing their further treatment.

Separate informed consent will also be taken for participation in the qualitative interviews. The main study consent form will include consent to be contacted for the qualitative interview (patients will be reminded that participation in the main study does not mean that they must participate in the qualitative interview). The qualitative researcher will select a sample of patients and the patient will be sent an interview study patient information sheet and a consent form. When the consent form has been received, the researcher will contact the patient to arrange a convenient time / location for interview. We also aim to interview patients who do not agree to take part in the main study. If a patient declines to participate in the main study, the personnel responsible for recruitment will invite them to take part in the interview study. If they agree, they will be given an interview study information sheet, study reply form, and consent form. These can be returned to the research team using a pre-paid self-addressed envelope.

We will comply with Welsh language requirements and the PIS, Consent Form and any other required participant documentation will be available in Welsh. However, all documentation used for data collection (i.e. outcome measures) will remain in English as they are designed and validated in English.

9.4 Registration

Eligible participants who have consented to take part in the study will be registered by recording key information including; contact details, past medical and medication history, as well as demographics.

10 Study Intervention

10.1 Decision aid

Results from the index tests collected from the first cohort will be used to develop a statistical model which will form the engine behind our clinical decision aid. This decision aid will combine results from the simple tests performed in primary care, to best predict urodynamic diagnosis (detrusor overactivity during bladder filling, bladder outlet obstruction and detrusor underactivity during voiding).

The presence or absence of nocturnal polyuria will not be included in this decision aid but will be separately assessed and included as an addendum to the diagnostic prediction. The resulting decision aid will provide probabilities for each of the three possible diagnoses. Qualitative work with expert consensus groups, conducted in parallel with the study will develop management decisions recommendations and thresholds for clinically useful diagnostic prediction in order to map the diagnoses predicted by the statistical model to current guidelines.

Acceptability of the decision aid to patients and clinicians will be assessed in the latter part of the study by use of a prototype decision aid. This prototype will be created using Shiny, a web application framework for the statistical programming language R. The prototype will be presented as an online tool, where the primary care staff input index test variables into an online form akin to the QRISK2® calculator (12). Once the form is submitted, a screen showing the index test results, and diagnostic probabilities and management recommendations will be displayed.

We will investigate the feasibility of automatic extraction of these test results, along with patient characteristics (demographics and other clinical), from the electronic record as well as the automated upload of these results into GPs' patient administration systems or simply saving as a document into the patient's record upon study completion.

10.2 Index tests

Our literature review (Oct 2015), updating the results of the NICE Guideline review, identified the investigations listed in Table 1 below as having potential value in diagnosing the cause of LUTS and which we will consider as index tests in the study.

Table 1

Test	*Details*	*Result*	*Visit*
Relevant demographics	Following assessment for eligibility and agreement to participate	Age in years	Identification/screening
Physical examination of abdomen	Carried out by competent primary care health professional. To palpate for a distended bladder.	Bladder palpable/not palpable	First GP consultation
Digital rectal examination	Carried out by competent primary care health professional. To determine prostate enlargement and likelihood of locally advanced prostate cancer.	Prostate mild/moderate/severe enlargement Further assessment for prostate cancer required/not required	First GP consultation
Prostate specific antigen	Single blood test. To compare value against NHS-defined thresholds	PSA value – established thresholds for further assessment for prostate cancer (typically > 3 ng/mL) or benign enlargement (typically ≥ 1.5 ng/mL) For decision aid: continuous variable in ng/mL	First GP consultation
ICIQ-Male LUTS* symptom questionnaire	Patient-completed validated questionnaire which defines presence, type and severity of LUTS	Total score (0-44); Voiding symptom score (0-20), storage symptom score (0-24), quality of life score (0-4).	Study Visit, Part A
IPSS questionnaire	Patient-completed validated questionnaire which defines presence, type and severity of LUTS	Total score (0-35)	Study Visit, Part A

Frequency volume chart*∞	A patient-completed/automated diary (at least 3 days) of the volumes and timing of urine passed.	Waking (day) time frequency, sleeping (night) time frequency, 24 hour voided volume, nocturnal voided volume, average volume voided each void	Given in Patient Information Pack - Patient completes at home
Uroflowmetry*	'A measurement of urine flow rate and voided volume as a function of time, either in the clinic or at home. Patients in the PriMUS study will perform uroflowmetry at home using the Flowtaker device.	Maximum flow rate, voided volume against normal age-adjusted range. Single value in mL/s	Given in Study Visit, Part B - Patient completes at home
Post void residual*	Simple abdominal ultrasound scan to determine the volume of urine remaining in the bladder after urination.	Residual volume against normal age-adjusted range. Single value in mL	At Study Visit , Part B

Table 1: Index tests to be used in model development. Non-discriminatory tests will be excluded in final model. *Not currently available and/or in routine use in Primary Care. ∞ Also used to characterise presence of nocturnal polyuria as an addendum

10.3 Reference test

The literature review confirmed invasive urodynamics (also known as filling and voiding cystometry) as the most appropriate diagnostic reference test for this study. The test involves passing a thin catheter into the patient's bladder, via the urethra, and another into the rectum, to measure intravesical and abdominal pressure respectively. Abdominal pressure is subtracted from intravesical pressure to give the pressure generated by the detrusor (bladder) muscle itself. Before commencing the test quality control checks are carried out including checking that pressure measurement is standardised by zeroing against atmospheric pressure; ensuring efficient subtraction of the abdominal pressure from the bladder pressure and ensuring that the detrusor (subtracted) pressure trace starts at zero. The detrusor pressure is then measured whilst the bladder is artificially filled with saline. During this time the bladder may show isolated (phasic) pressure rises diagnostic of detrusor overactivity. Once the patient's bladder is full, he passes urine into a flowmeter which measures urine volume and flow rate. Residual urine is measured at the end by ultrasound. Variables of interest

include detrusor pressure during filling (P_{det}), maximum urine flow rate (Q_{max}), detrusor pressure at the point of maximum flow ($P_{detQmax}$), voided volume (V_{void}) and residual volume. All these measurements are read directly from the cystometric or flow recording. Using these measurements urodynamics defines the presence or absence of three conditions: detrusor overactivity during filling, and bladder outlet obstruction and detrusor underactivity during voiding [6]. Absence of these three diagnoses will classify the individual as having normal urodynamics. The three conditions, which can co-exist, have definitions standardised by the International Continence Society [6,7] as follows:

Detrusor overactivity: A urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked and which are signified by a phasic (transient) detrusor pressure rise during bladder filling associated with a sensation of urgency

Bladder outlet obstruction: $P_{detQmax} - 2Q_{max} > 40$ (bladder outlet obstruction index; BOOI)

Detrusor underactivity: $P_{detQmax} + 5_{Qmax} < 100$ (bladder contractility index; BCI)

Nocturnal polyuria: It is defined as a night-time urine volume output that is > 33% of that during the whole of a respective 24-hour period [4]. This will be separately flagged up as an additional identified relevant condition using variables from the frequency/volume chart.

10.4 Compliance

A monitoring plan to assess compliance of the reference urodynamic testing will be in place. In summary, the data for the first 4 participants in each hub will be reviewed, followed by 1 in 5 for the next 25 participants in each hub. Monitoring of urodynamic test will then be conducted for every 10%. The data will be reviewed by the urologist(s) and clinical scientists on the research team. Any discrepancies will be reviewed and further training conducted.

11 Study Procedures

All participants will be enrolled in the study for up to 6 months, from baseline to 6 month post-clinical assessments.

Patients will either present to their GP in an initial GP consultation visit with one or more bothersome LUTS, or they will be identified through database searches and invited to take part in the study.

Patients presenting to their GP with one or more bothersome LUTS

Patients initially presenting to their GP with one or more bothersome LUTS, will be assessed for eligibility and provided with a patient information pack (i.e Patient Information Sheet, Patient

Information Leaflet, Consent Form, Urodynamics Leaflet and Frequency Volume Chart). The right of the patient to refuse consent without giving reasons will be respected throughout the study. Furthermore, the patient will be free to withdraw from the study at any time without giving reasons and without prejudicing further treatment.

The GP will follow NICE guidelines (http://www.nice.org.uk/guidance/cg97) and will complete the following index tests:

- Physical Examination
- Digital Rectal Examination (DRE)
- Prostate Specific Antigen (PSA) Test

The GP will complete and sign the Patient Eligibility Checklist, confirming the patient has met the criteria to enter the study. The GP can consent the patient within the initial visit, if they feel that this is appropriate. Otherwise, the potential participant will be required to complete and sign the Consent to Contact Form, confirming they are happy to be contacted by the research nurse and ensuring the responsible research nurse has their up to date contact details.

The GP will then pass the two documents to the site research nurse, to ensure they have the contact details needed to telephone the potential participant and confirmation of the patient's eligibility. GPs will also complete and sign the Patient Eligibility Results Form, documenting the results of the three index tests conducted in the initial consultation.

The participant will be given adequate time to consider taking part in the study, before being invited to attend a Study Visit (Part A and B). A research nurse will then call the potential participant, using contact details from the Consent to Contact Form and establish whether they would like to enter the study. If the potential participant agrees to enter the study during the phone call with the research nurse, they will arrange a Study Visit date. The research nurse will also instruct the patient to complete the Frequency Volume Chart, for at least 3 days, to record the volumes and timing of urine passed. prior to their Study Visit, Part A. If the potential participant decides not to enter the study, the research nurse will ask the potential participant whether they would be interested in having an informal interview. If this is something the patient is willing to consider, the research nurse will arrange to send out the separate qualitative patient information pack (including the Patient Information Sheet and Consent Form) to the potential participant. This will include a self-addressed envelope to send their completed consent form back to the research team.

Patient identified by Database Searches

Patients identified through a database search will be sent a letter from their GP (PriMUS Potential Participant Letter), informing the patient of the study and inviting them to take part. These patients will be provided with the Patient Information Summary Leaflet and the details of their local research nurse to contact, if they are interested in entering the study.

Study Visit

The Study Visit can be separated into two parts, Part A and Part B. Part A and Part B can either be completed on the same day, or separated into two separate visits.

Part A

During Part A, the patient will be asked to sign the consent form (unless already been consented during the initial GP consultation). They will complete the ICIQ – Males LUTS Symptom Questionnaire and the IPSS questionnaire. The research nurse will complete the remaining index tests by completing the corresponding CRFs.

Part B

Part B, will be dedicated to completing the reference test (urodynamics). Following completion of this procedure, research nurses will appropriately debrief the patient, providing the patient with the Post Urodynamic Leaflet and Patient Safety Card, answering any questions the patient may have.

The patients will also be provided with a uroflowmetry device (home flow meter) (Flowtaker, http://www.laborie.com/products/flowtaker/), along with specific instructions for how to use this at home. The research nurse will instruct the patient not use the uroflowmetry device until they have received specific direction to use it during the post-urodynamics safety phone call. The patient will then drop the device back to the GP Practice within two weeks. If the patient is unable to do this, they will be provided with packaging to post the device back within two weeks.

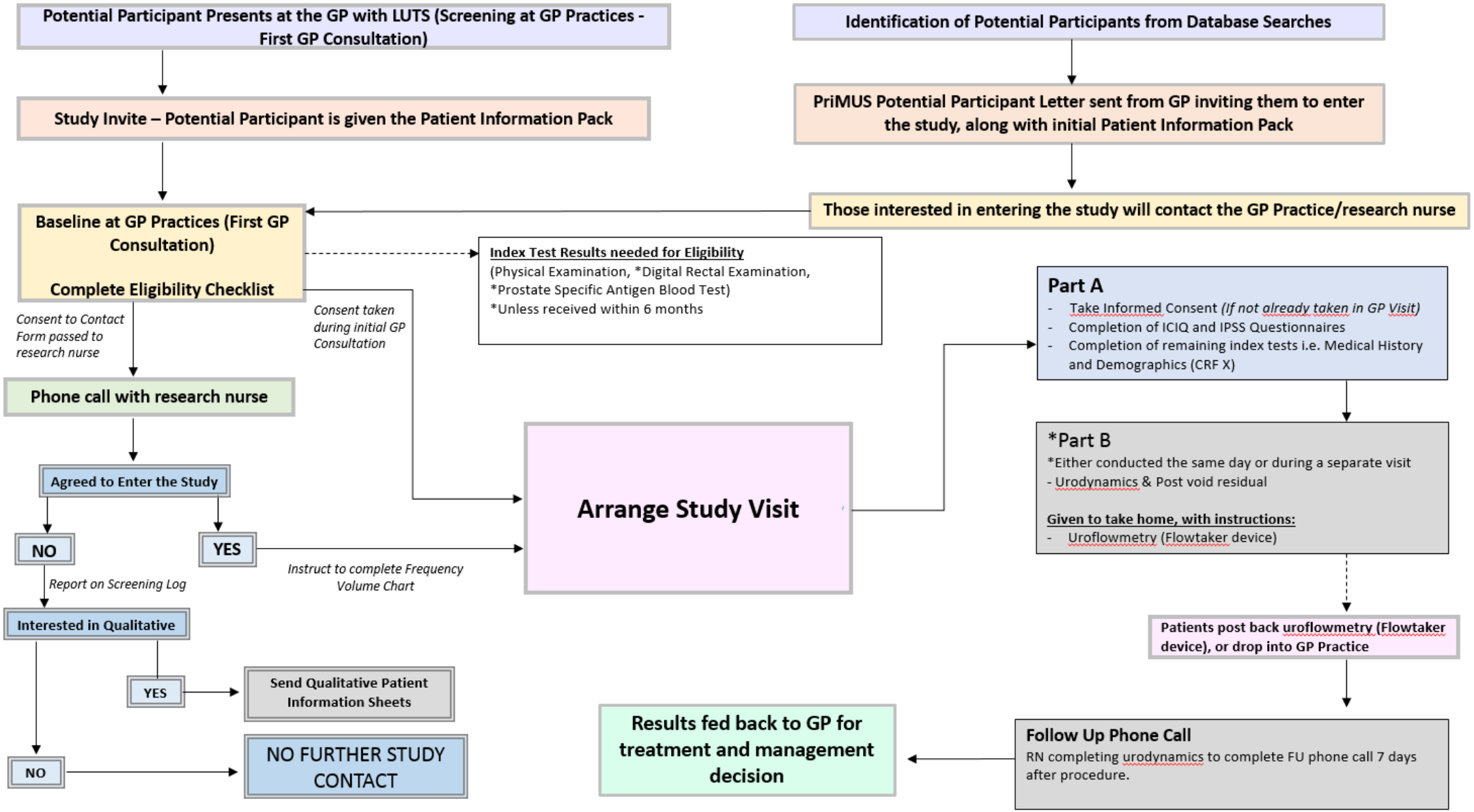
3 Day Follow Up Phone Call

Research nurses performing the urodynamics reference test will be responsible for conducting a follow up phone call to the patient 3 days following the procedure. The research nurse will be required to complete the corresponding 3 Day Follow Up Phone Call CRF and work their way through the form with the patient, ensuring that any adverse event is documented. If the patient appears to have an infection, the research nurse should advise them to organise and attend a GP visit. If there is no indication of infection, research nurses will instruct the patient to begin using the uroflowmetry device.

Results

Results from the uroflowmetry and urodynamics will be compiled and fed back to the GP via secure fax or email where the GP will be responsible for following up the patient as appropriate. Guidance on further management and treatment decisions will be provided to GPs, but the clinical management of the patient is at the discretion of their treating clinician.

The participants' NHS medical notes will be reviewed at approximately 3-6 months post assessment to record the clinical management and treatment decisions.


Potential Participant Presents at the GP with LUTS (Screening at GP Practices - First GP Consultation)
Identification of Potential Participants from Database Searches
Study Invite – Potential Participant is given the Patient Information Pack
PriMUS Potential Participant Letter sent from GP inviting them to enter the study, along with initial Patient Information Pack
Those interested in entering the study will contact the GP Practice/research nurse
Baseline at GP Practices (First GP Consultation)
Complete Eligibility Checklist
Index Test Results needed for Eligibility
(Physical Examination, *Digital Rectal Examination,
*Prostate Specific Antigen Blood Test)
*Unless received within 6 months
Consent to Contact Form passed to research nurse
Consent taken during initial GP Consultation
Part A
- Take Informed Consent (If not already taken in GP Visit)
- Completion of ICIQ and IPSS Questionnaires
- Completion of remaining index tests i.e. Medical History and Demographics (CRF X)
Phone call with research nurse
Agreed to Enter the Study
Arrange Study Visit
*Part B
*Either conducted the same day or during a separate visit
- Urodynamics & Post void residual
Given to take home, with instructions:
- Uroflowmetry (Flowtaker device)
NO
YES
Report on Screening Log
Instruct to complete Frequency Volume Chart
Interested in Qualitative
Patients post back uroflowmetry (Flowtaker device), or drop into GP Practice
YES
Send Qualitative Patient Information Sheets
NO
NO FURTHER STUDY CONTACT
Results fed back to GP for treatment and management decision
Follow Up Phone Call
RN completing urodynamics to complete FU phone call 7 days after procedure.

11.1 Training of Staff

All staff involved in the study specific procedures (including recruitment/consent, collection of study data, application of intervention and clinical assessments) will be trained in the relevant aspects of GCP.

All relevant staff at sites will receive training to ensure they understand the PriMUS study protocol and how to identify potential participants. All staff at each site with delegated responsibilities for any aspect of the PriMUS study will be provided suitable training to ensure they understand the study procedures.

Clinicians responsible for making management decisions will be given guidance and training on the clinical management scenarios, but will be free to manage the patient using their own clinical judgement.

Research Nurses involved in performing urodynamics will be required to have sufficient clinical and study training. They will preferably have completed a recognised urodynamic course (e.g. https://www.nbt.nhs.uk/bristol-urological-institute/bui-education/certificate-urodynamics-course). Each of the three research hubs will have a urology 'champion' who will be available during the period of the study to answer any urgent clinical queries following the urodynamic procedure. Throughout the study there will be an element of peer support offered by members of the study clinical team.

All urodynamic training will be overseen by the urologists and personnel will be signed off once deemed fully trained. A researcher manual will be provided, which will document the study-specific processes in detail, including full instructions of how to use the equipment. Upon completion of this training, personnel should file relevant proof of training and certificates into the site file.

Sites will receive a full training manual, which will document all study-specific processes in detail, which will be used as part of the site initiation training.

11.2 Clinical Assessments /Data Collection

For men who are willing and consent to participate, results of the required index and reference tests will be recorded as they are performed. This will be co-ordinated by the research nurse for the study at each hub aided by primary care records and Research Network support. GPs will complete the Patient Eligibility Checklist, which will confirm that the patient is eligible to enter the study. The results of these tests will not be detailed on the Patient Eligibility Checklist. Data collected from the index tests performed by the GP during the first GP consultation will be documented on the Patient Eligibility

Results form. The potential participants will be required to complete and sign a Consent to Contact Form, confirming that they are happy to be contacted by the research nurse and giving permission for their medical records to be reviewed, so that research nurses can follow up any results of the index tests that aren't readily available immediately following the initial GP consultation (i.e. PSA test).

The results of the tests will be compiled into a results report form, which will subsequently be sent to the GP for further symptom management. The study research nurse performing the urodynamics will not have knowledge of all the results of the index tests when performing and analysing the reference test, only those needed to inform the urodynamic procedure.

As detailed in Table 2 below, the minimum dataset will comprise: age (years), bladder exam (palpable/not palpable), digital rectal exam (mild/moderate/severe enlargement), PSA (≥1.5 pg/mL or <1.5pg/mL) and as an absolute value, symptom score with storage, filling and QoL components, uroflowmetry (Q_{max} in mL/s and V_{void} in mL), residual volume (mL), frequency volume chart [Waking (day) time frequency, sleeping (night) time frequency, 24 hour voided volume, average voided volume, nocturnal voided volume]. The variables from urodynamics will include a 3-item quality control checklist; zeroed to atmospheric pressure, adequate subtraction of abdominal pressure and detrusor pressure starting at zero (+/- 5 cmH_2O), detrusor overactivity on filling (Yes/No), BOOI (>40 or ≤40), BCI (< 100 or ≥100), and absolute values for both BOOI and BCI.

Table 2		Initial GP Consultation		Study Visit (Either 1 Visit or 2 Separate Visits)	
Procedures	**Description and Documentation**	**Screening**	**Baseline**	**Part 1 (Consent, Questionnaires and home tests, and Remainder of Index Tests, if not performed at GP visit)**	**Part 2 (Reference Test Urodynamics)**
Patient Documentation and Baseline CRF collection					
Eligibility assessment	Patients who patient with LUTS will be assessed by GP for eligibility	X			
Patient Information Pack	Patients who present at the GP with LUTS will be given a patient information pack, this includes the frequency volume chart	X			
Informed consent	Patients will be invited back to the site to give informed consent		(X)	X	
Index Tests and Flowmetry					
Demographics	Collection of demographical data including ethnicity			X	
Medical history	Your age, BMI, symptom duration, treatment history and any other relevant medical history will be recorded			X	
Physical Examination	An examination of your abdomen and genitals.		X		
Digital rectal examination	A gloved, lubricated finger will be inserted into patients back passage so that the prostate can be examined.		X		
*Prostate specific antigen blood (PSA) test	A test to measure the amount of prostate specific antigen in the blood. A raised level may be an indication of prostate cancer, but may also be due to non-cancerous enlargement or inflammation of the prostate.		X		
Frequency volume chart	A patient-completed/automated diary (at least 3 days) of the volumes and timing of urine passed.		X (Given in Patient Information Pack, completed at home)		

Uroflowmetry	Provided with a home flowmeter, for patients use at home: a measurement of urine flow rate and voided volume as a function of time using a simple meter.				X (Given in this visit, completed at home)
Post void residual	Simple abdominal ultrasound scan to determine the volume of urine remaining in the bladder after urination.				X
Questionnaires					
ICIQ-Male LUTS* symptom questionnaire	Patient-completed validated questionnaire which defines presence, type and severity of LUTS			X	
IPSS questionnaire	Patient-completed validated questionnaire which defines presence, type and severity of LUTS			X	
Reference test					
**Urodynamics	This is the most invasive test involved in the study and carries a small risk of a bladder infection (under 'Expected Adverse Events From Urodynamics' details below), but it also gives the best information about what is causing the urinary symptoms.				X

*PSA test – within the previous 6 months prior to baseline visit

**Urodynamics – within the last 6 months (providing the data meets the Quality Control 3 – item checklist within our specification)

11.3 Follow-up

The participants will be followed up at approximately 3-6 months after their second visit (following the urodynamics reference test). Follow up will ascertain the management decisions that have been made by the GP after considering results and recommendations from the index and reference tests.

As a minimum requirement, we will collect the decisions regarding medical treatment and referral rates. We will also collect information regarding any study specific adverse events that have been experienced, as well as ensuring that all serious adverse events have been captured and reported.

A review of medical notes will be done by the research nurses to establish and report decisions in relation to advice and recommendations given to the patient regarding things like lifestyle changes.

12 Withdrawal & Loss to Follow-Up

12.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the study at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the study.

If a participant initially consents but subsequently withdraws from the study, clear distinction must be made as to what aspect of the study the participant is withdrawing from. These aspects could be:

1. Withdrawal from index tests / reference test
2. Withdrawal from NHS medical note review
3. Withdrawal of Consent to all of the above

The withdrawal of participant consent shall not affect the study activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly:

If a participant wishes to stop taking part in the study completely, they may need to be seen one last time for an assessment.

A participant may withdraw or be withdrawn from the study for the following reasons:

- Withdrawal of consent for investigation by the participant

- Any alteration in the participant's condition which justifies the discontinuation of the intervention in the Investigator's opinion
- Non-compliance

In all instances participants who consent and subsequently withdraw should complete a withdrawal form (see Withdrawal Form in study pack) or the withdrawal form should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. This withdrawal form should be sent to the Study Manager. Any queries relating to potential withdrawal of a participant should be forwarded to Study Manager.

12.2 Loss to follow up

It is essential for the study that every man recruited completes all the assessments, particularly the urodynamic reference assessment. We will make every effort to ensure that each participant completes the assessments by emphasising the importance of obtaining a full data set (including urodynamic assessments). We will also arrange to complete the assessments at a time that is convenient to them so they will not have to travel far. At enrolment patients will be asked to provide contact details for members of the research team to contact while attempting to make assessment appointments. Participants will also consent to the research team communicating with their GP.

- Participants will be identified as lost to follow-up if it is not possible to contact them directly or via their GP for 6 weeks post consent.

13 Internal Pilot and Progression Criteria

We will conduct an internal pilot phase over the first six - nine months of the recruitment phase (study months 6 – 15) (see criteria in Table 3 below).

The internal pilot phase will assess the site and patient recruitment rate, proportion of patients undergoing urodynamic assessments and those with a complete data set for analysis. The progression criteria have been designed to allow for mitigating strategies to be discussed to allow for some adaptation to recruitment processes. We will discuss the results with our Study Steering Committee, before reporting to the NIHR HTA Programme at Month 15, for permission to proceed.

In accordance with the HTA guidance on internal pilot studies, we will exclude the first two months of recruitment from our calculation of the recruitment rate as we anticipate a 'lag phase' during which practices are still being registered and participating clinicians develop confidence and competence in recruiting patients. We will constantly be assessing the criteria during the internal phase. We will also

conduct a qualitative evaluation of the acceptability of the gold standard urodynamic assessment with patients, and feedback from these interviews will assist with any refinement in processes during the pilot phase. We will also assess the prevalence of the three urodynamic diagnoses, this will ensure that we have powered the study correctly.

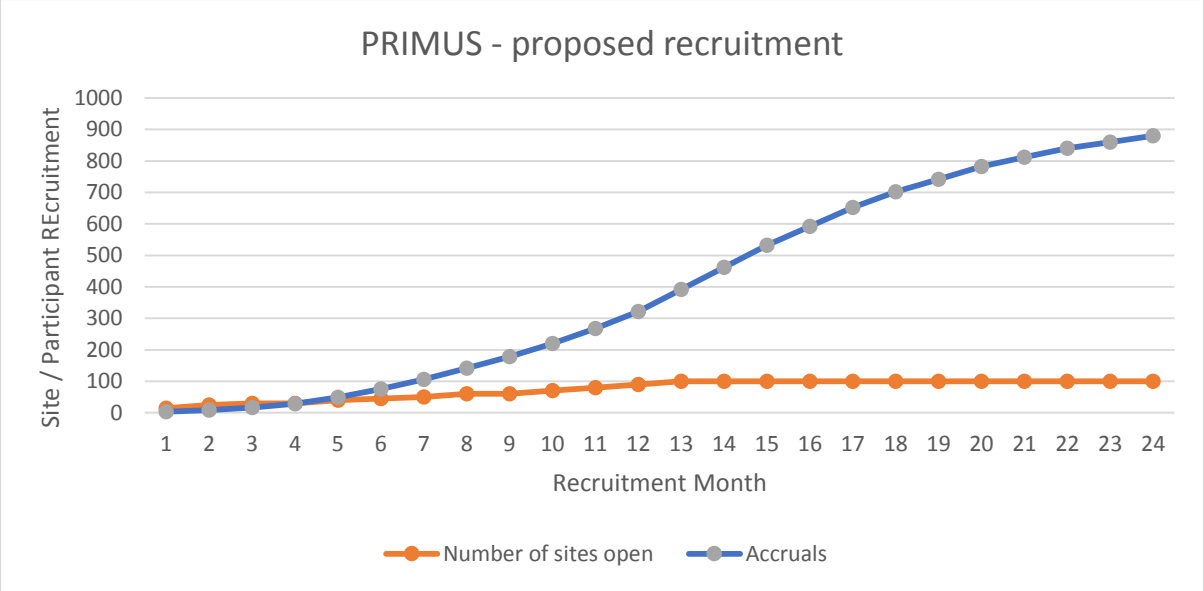
Table 3: Progression Criteria

Criteria	Level	Action
Site Recruitment	30 sites open	Monitor site recruitment and time to first recruit. At least 0.3 patients per practice per month. Discuss potential mitigating strategies
Recruitment rate*	70 % 40 – 70% < 40%	GO Discuss potential mitigating strategies STOP?
Gold standard undertaking (and evaluable?)	70 % 50 – 70% <50%	GO Discuss potential mitigating strategies STOP?
Acceptability of gold standard urodynamic assessment	Qualitative interviews	

**Allowing for 2 –month lag phase*

13.1 Recruitment rates

We plan to screen an average of 147 and recruit 37 men per month on average during recruitment with predicted numbers lower in initial, and higher in later phases of recruitment. From CPRD 2014 data we estimate an incidence of four men per practice per month. Target accrual rates are presented in the Figure below:



14 Qualitative Data Collection

14.1 Internal pilot phase qualitative evaluation

A qualitative evaluation will be included in the internal pilot. The aims of this qualitative evaluation will be to:

- Assess patients' acceptability of the reference urodynamic assessment, identifying barriers / facilitators to the uptake of, or satisfaction with the test
- Understand patients' experiences of lower urinary tract symptoms, their management of the symptoms/condition, their decision to seek medical advice, and the factors that matter most to patients
- Identify other barriers / facilitators to participation in the study (from perspective of both healthcare professionals and patients)
- Identify themes relating to positive and negative experiences of taking part in the study (from perspective of both healthcare professionals and patients)
- Use the results to inform strategies that will maximise recruitment and retention

Semi-structured interviews will be carried out with patients recruited to the main study to gather in-depth information on their experience of participating in the study. We will also interview a sample of patients who declined to participate in the main study. Interviews will also be conducted with healthcare professionals that are involved in recruiting / consulting with patients invited to / taking part in the study. These will be conducted face-to-face or by telephone.

Participants and recruitment

Qualitative evaluation will be conducted with 12-15 patients who agree to participate in the main study (during the pilot phase). The patient consent form for participation in the main study will include consent to be contacted for the qualitative interview. Patients will be selected to ensure representation from different general practices, across the three study regions (Wales Primary Care Research Network; North East England and North Cumbria Research Network; Western Research Network). The patients selected will be contacted within two weeks following their second research visit (during which they will undergo the reference test - urodynamics), to invite them to take part in an interview. If they agree, they will be sent an interview study patient information sheet and a consent form, which they will need to return to the research team. A convenient time / location will be arranged for the researcher to interview them. We will also conduct qualitative interviews with approximately 5 patients who declined to participate in the main study. Recruiting healthcare professionals will invite these individuals to take part in a short interview study; those who agree will be given an interview study patient information sheet, study reply form, and consent form, which they will return to the research team if they want to participate. A researcher will then contact them to arrange a convenient time / location for an interview.

We will also conduct interviews with 10-15 healthcare professionals (ensuring representation from each study region, to account for local recruitment/study differences). We will write to the participating general practices to inform them about the qualitative pilot work, and to ask them to identify individual healthcare professionals that would be interested in taking part in an interview. We will telephone the practices to obtain a list of interested individuals. We will then contact the healthcare professionals directly to arrange a convenient time and location for the interview (anticipate that these interviews will take place towards the end of the pilot-phase to allow sufficient experience of recruiting patients). Written consent will be obtained for face-to-face interviews. Consent will be given verbally for telephone interviews (verbal consent will be audio recorded).

Data collection and analysis

A trained qualitative researcher will conduct the interviews. Prior to conducting the interviews, the researcher will make sure that consent (written or verbal consent) has been received, and they will briefly outline what the interviews will involve. All the interviews will be audio-recorded and transcribed verbatim. The qualitative researcher conducting the telephone interviews will also ensure that verbal consent is audio-recorded. It is anticipated that the interviews will last approximately 30-45 minutes. The interviewer will use a flexible semi-structured interview guide to ensure the essential

information is gathered, whilst allowing the interviewer flexibility to explore emerging themes. Broadly, interviews will assess practicality and acceptability of conducting urodynamics.

The patient interview guide will explore patients' reactions to the test (e.g. How did you feel about having the test? What was your experience of that test? Did you have any concerns? Was it better/worse than anticipated? Were there any problems/delays? Did you think it was useful? How might the process be improved?), and also their experience of the recruitment and study process (e.g. How were you asked to take part in the study? Do you think you were given the right information about urodynamics beforehand? Was there anything that might put people off taking part?). The interview guide will also explore the patient's experience of having LUTS and of managing their symptoms / condition, the factors influencing their decision to seek medical advice, and the factors that matter most to them when managing the symptoms or making a decision about the management of the condition.

The clinician interview guide will explore the general practitioners' experiences of the study recruitment process (e.g. any difficulties experienced approaching the discussion of having urodynamics), and also insights into their patients' responses to the process and the urodynamic assessment (if known, e.g. a patient might have discussed their concerns about the urodynamic assessment with their general practitioner).

Interview transcripts will be analysed thematically using NVivo qualitative analysis software. A coding framework will be developed based on the pre-defined themes included in the topic guide, and new themes emerging from the data. In-depth qualitative research during the pilot phase will allow us to identify problems that might undermine the acceptability of the study, particularly undertaking urodynamic tests, and to develop strategies that will maximise recruitment and retention. It will also provide us with a more detailed understanding of how the men experience the symptoms / management of LUTS, and the factors that matter to them as patients with this condition.

14.2 Development of Management recommendations

A group of 20-25 stakeholders will attend a consensus meeting during Autumn 2017. This will include urologists, GPs and men with LUTS either as separate groups or in a plenary. The co-applicants from these stakeholder sections (urology, PPI, primary care) will undertake to invite and recruit these members, and we will liaise closely with patient representative groups. The participating clinicians will be presented with a number of clinical case scenarios ($n \approx 16$), where they will be asked to consider

how they could be managed (using standard RAND methodology). Group facilitation and the methods used to elicit opinions on treatment management will be carefully planned to ensure that the opinions of all of the stakeholders are elicited, and considered. This group will also be contacted at times during the study for comment, interpretation of preliminary conclusions, and for input into aspects of the management recommendations etc. In this way the group will be informed about study progress, and be able to provide further feedback, thus operating as a "Reference Group". We propose also to re-convene the Consensus / Reference group towards the end of the data interpretation phase (including the assessment of qualitative data about feasibility and likely implementation) for additional feedback, and to contribute to planning of a subsequent implementation / evaluation study application. The later meeting will also examine potential for early impact from the findings as they stand, with publicity to patients, patient groups, GPs, other staff, and management / commissioning groups where actionable findings are evident. Throughout the process we will take specific steps to support the patient and PPI representatives to feel confident to contribute.

14.3 Tool usability and acceptability

Interviews will be conducted with GPs who will be the main clinician group using the decision aid to inform management discussions with their patients. We aim to recruit a total of 30 general practitioners across the three study hubs (ten interviews per hub). We plan to use a 'think aloud' protocol and a semi-structured interview guide to initially explore clinicians' opinions on the optimum characteristics of the design aid, its potential use in routine practice over a number of different diagnostic scenarios and in the later stages of the study, their reactions to the prototype decision aid. The 'think-aloud' method is commonly used for usability testing, and involves participants thinking aloud as they perform a task [8]. 'Think-aloud' verbalisations will be audio-recorded and transcribed for analysis. The clinicians will then take part in a short semi-structured interview (30-60 minutes). The interview guide will cover the following topics (expanding on topics already discussed during the 'think-aloud' protocol): diagnostic aid design; user-friendliness; use with patients; fit of inputs and outputs with local clinical systems (including information technology systems); potential influence on clinicians' behaviour (i.e. decision making and setting of diagnostic accuracy thresholds); problems encountered/perceived; unexpected consequences; perceived benefits of decision aid; contextual factors that might impact use or future implementation. Interviews will also be conducted with a sample of patients participating in the study. We aim to conduct 30 patient interviews (ten interviews per hub) between 2-4 weeks after their initial management has been decided. These patients will be presented with a prototype example of the diagnostic decision aid and will be told how it will be used to inform the management discussion with a GP. The standard care pathway will also be presented to patients as a comparison to the proposed alternative pathway, which will include locality of care and

average wait times. Using these hypothetical scenarios, we will conduct semi-structured interviews to assess potential acceptability to patients, and feasibility of introducing the decision aid into primary care.

14.4 Referral Rates

We will ascertain the number of men recommended for referral by GPs who used the output of the prediction model and considered the management options recommended and compare this with 5-year data from the Clinical Practice Research Datalink (CPRD; historical control) to estimate potential impact of the aid on referral rates. The CPRD holds anonymised primary care records from almost 700 practices across the UK and by July 2013 had abstracted data from primary care records stored by a variety of bespoke GP systems for almost 12 million patients with median follow-up of 5.1 years and [9]. The CPRD has previously been used to define cohorts of men with benign prostatic hypertrophy for epidemiological studies [10, 11]. We will use the CPRD to estimate recent trends in referral rates for men presenting to UK primary care with an incident episode of LUTS. For these historical control data, our denominator will consist of men aged 16 and over whose primary care records contain a Read code indicating an incident presentation with LUTS. We will define incident presentations as those without a prescription for an alpha-blocker (except doxazosin), 5-alpha reductase inhibitor or combination drug at the time of incident presentation and without a LUTS related Read code in the preceding 365 days. Where doxazosin is prescribed, we will only include men who have a Read code for hypertension and no prior record of LUTS. To include only probable benign cases, we will exclude men with a Read code suggesting a urological malignancy, haematuria, urinary tract infection or a prostate specific antigen above the age-specific reference range within 28 days after incident LUTS presentation. Our numerator will consist of men from our denominator whose primary care records contain a Read code indicating referral to specialist urology services within 28 days of the incident LUTS presentation. This short time period is to increase likelihood that referral is due to initial presentation and not to treatment failure. We will describe referral rates over time and by age-group and compare these with the referral rate occurring during practice participation in the PriMUS study to understand the potential impact of widespread use of the aid on secondary care services. We will specify the assumption that this referral rate reflects decisions based on the reference standard urodynamic result, and will model variations on this according to the observed accuracy of the decision aid in the validation study.

15 Safety Reporting

The Principal Investigator is responsible for ensuring that all site staff involved in this study are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI/local researcher at the participating site to the CTR unless the SAE is specified as not requiring immediate reporting (see section 15.2).

15.1 Definitions

Term	Definition
Adverse Event (AE)	For the purpose of this study an adverse event will be defined as only the specific AEs as detailed in section 15.2.
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the study participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

An SAE occurring to a research participant should be reported to the main REC where in the opinion of the CI the event was:

• Related – that is, it resulted from administration of any of the research procedures, and

• Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence

15.2 Study Specific AE reporting requirements

For the purposes of this study the following events will be considered AEs and must be captured on the CRF form.

- Urinary tract infection
- Haematuria
- Urinary retention
- Discomfort
- Dysuria

These should be completed in the participant's notes and on the AE reporting CRF page and forwarded to the CTR in the normal timeframes for CRFs.

15.3 Study Specific SAE Reporting requirements

In addition to the SAE reporting requirements above, for the purposes of this study the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR PriMUS Study Team within 24 hours of knowledge of the event:

- Urethral trauma requiring intervention

15.3 Causality

Causal relationship will be assessed for the clinical and data collection procedures. For AEs, this assignment should be made by the PI or the delegated research nurse. For SAEs this assignment should be made by the PI or delegated research nurse and the assessment confirmed by the Chief Investigator or a delegated Clinical Reviewer.

Relationship	Description	Reasonable possibility that the SAE may have been caused by the intervention?
Unrelated	There is no evidence of any causal relationship with the study/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the study/intervention (e.g. the event did not occur within a reasonable time after administration of the study medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the study/intervention (e.g. because the event occurs within a reasonable time after administration of the study medication). However, the influence of other factors may	Yes

	have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

15.4 Expectedness

The Chief Investigator(s) (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness. Expectedness decisions can be guided by the information in Table 4 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 in the table below is considered unexpected.

Table 4: Expected Adverse Events from Urodynamic Procedure

Expected Adverse Events From Urodynamic Procedure			
Adverse Event	Mild	Moderate	Severe
Urinary Tract Infection	Transient symptoms not requiring action	Persistent symptoms requiring participant to be seen by HCP with or without treatment (such as course of antibiotics)	Needing hospitalisation
Visible haematuria	Transient symptoms not requiring action	Persistent symptoms requiring participant to be seen by HCP with or without treatment (such as course of antibiotics)	Needing hospitalisation
Urinary retention	Transient symptoms not requiring action	Persistent symptoms requiring participant to be seen by HCP with or without treatment (such as course of antibiotics)	Needing hospitalisation

Discomfort on passing urine	Transient symptoms not requiring action	Persistent symptoms requiring participant to be seen by HCP with or without treatment (such as course of antibiotics)	Needing hospitalisation
Urethral trauma during insertion or removal of catheter for urodynamic procedure	Transient symptoms not requiring action	Persistent symptoms requiring participant to be seen by HCP with or without treatment (such as course of antibiotics)	Needing hospitalisation

15.5 Reporting procedures

15.5.1 Participating Site Responsibilities

The PI (or delegated research nurse from the study team registered on the delegation log) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR PriMUS Study Team within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by study number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

PRIMUS@cardiff.ac.uk

SAE Fax number:

0203 107 0840

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including 7 days after the participant receives the urodynamic assessments.

An SAE form is not considered as complete unless the following details are provided:

- Full participant study number
- The adverse event
- A completed assessment of the seriousness, and causality as performed by the PI (or delegated research nurse from the study team).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

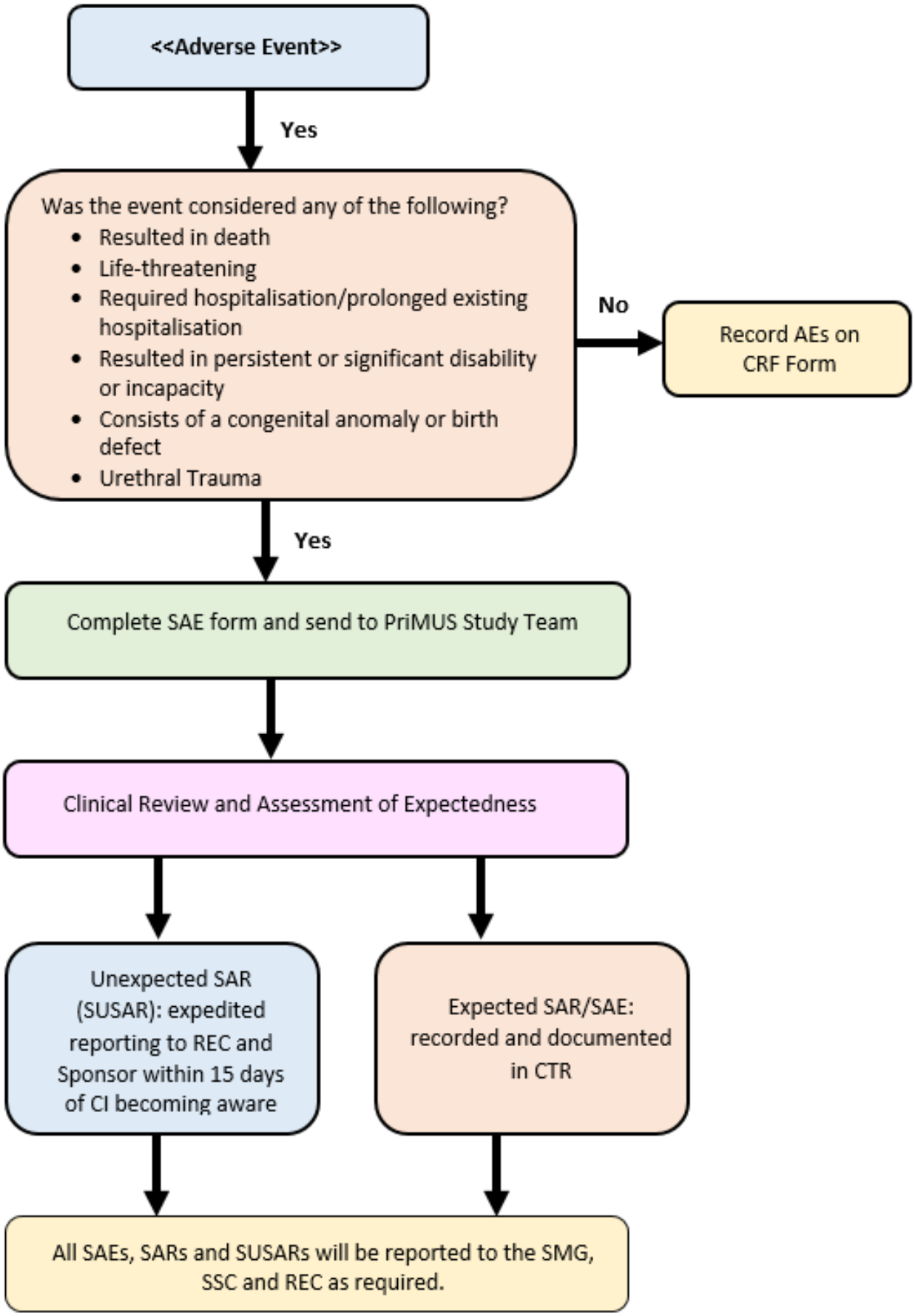
All other AEs should be reported on the CRF following the CRF procedure described in Section 15.

15.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form. The CTR should continue reporting SAEs until 7 days after the participant receives the urodynamic reference test. Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator(s) (or their delegate) for an assessment of expectedness.

CTR will notify the main REC of all related and unexpected SAEs (i.e. all unexpected SARs) occurring during the study within **15** calendar days of the CI becoming aware of the event. All SAEs and SARs will be reported to the monitoring committees (SMG and SSC) as required by the relevant committee/party. All unrelated SAEs will be reported to the SMG and SSC, and any arising safety concerns will also be reported to the main REC as part of the annual progress report.

SAE Flowchart (Figure 3)



15.6 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a study against any immediate hazard to their health or safety. Any urgent safety measure relating to this study must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

16 Statistical Considerations

16.1 Sample size

Development cohort: We will fit three separate dichotomous logistic regression models (Figure 2) to predict the presence of each of the conditions: Bladder outlet obstruction (BOO), detrusor overactivity (DO), and detrusor underactivity (DU).

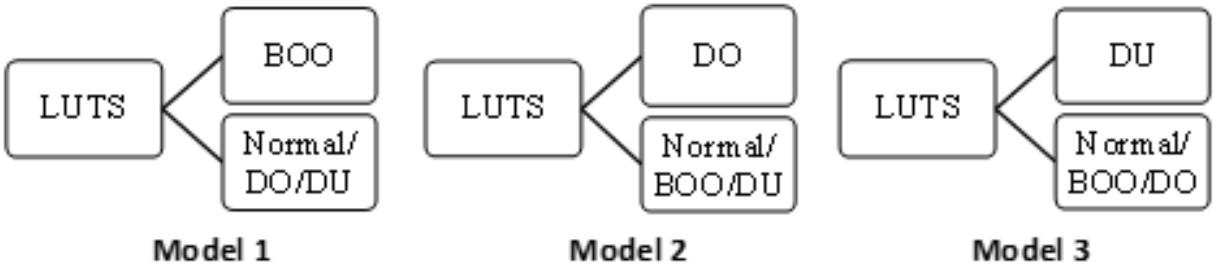


***Figure 2*:** Modelling strategy based on separate dichotomous logistic regression models. BOO, bladder outlet obstruction; DO, detrusor overactivity; DU, detrusor underactivity; LUTS, lower urinary tract symptoms.

Sample sizes for developing predictive models are typically based on ensuring that overfitting does not occur, and are based on rules of thumb discerned from simulation studies. The most commonly used rule suggests 10 events are required per predictor and was based on two simulation studies. Vittinghoff and McCulloch have undertaken more extensive evaluation, and suggest that this rule of thumb may be too conservative and can be relaxed as other factors are likely to be equally or more important than the number of events per predictor [12]. They suggest that events per predictor values (EPV) of between 5 and 9 may be justified. Of the four diagnosis categories, the lowest prevalence is estimated at 16% for DU, such that a sample of 350 would provide 56 events – enough assuming EPV = 5 for up to 11 variables to be fitted as required. Over 100 events would be expected for the BOO model and 200 for the DO model providing more than adequate events.

Validation cohort: The sample size for the validation study is determined by ensuring that estimates of test accuracy (particularly sensitivity) are made with adequate precision. Based on a sample size of

325, estimates of a sensitivity of 75% for DU, BOO and DO will be based on samples of 52, 101 and 185, and made within confidence limits of 14%, 10% and 8% respectively (based on the lower limit of the 95% confidence interval for an observed proportion of 0.75). Should the test be more sensitive, the confidence intervals will be narrower. Estimates of specificity for DU, BOO and DO will be based on samples of 273, 224 and 140 respectively. In the same way a specificity of 75% would be estimated within 6%, 7% and 8% intervals.

To complete the study we require 675 complete data sets. We plan to screen 3520 men with an expected 25% (880 men) agreeing to take part. This allows an attrition rate of a further 20-25% of these to achieve 675 complete datasets; 350 in the development cohort and 325 in the validation cohort.

16.2 Missing, unused & spurious data

We will ensure that missing data is kept to a minimum. Results of all index and reference tests will be recorded. We will investigate patterns of missingness in the development and validation cohorts because if a predictor is difficult to obtain in practice, then the model including it may not be of clinical relevance. In the event of missing data, multiple imputation will be used to impute missing values in order to avoid bias and make best use of the data, by replacing missing values with plausible values based on the distribution of the observed data.

Full detail will be provided in the Statistical Analysis Plan (SAP).

16.3 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

16.4 Termination of the Study

Progression criteria for the internal pilot phase is described in section 13. There is potential for the study to terminate early if our funder assesses the study as not being feasible following an assessment of progress against our targets at the end of the internal pilot with input from our SSC.

16.5 Inclusion in analysis

All participants with reference test data will be included in the analysis.

17 Analysis

17.1 Diagnostic prediction model

We have chosen to use three separate logistic regression models to develop numerical tools that will predict the urodynamic causes of LUTs using variables gathered by simple community-based tests. An alternative approach would be to use multinomial regression to investigate factors influencing the three diagnoses simultaneously, but such models require larger sample sizes to estimate the multiple parameters required [13]. For example, 11 predictors and three conditions would require 24 parameters which is not feasible in terms of cost and recruitment period. We will investigate patterns of missingness in the development and validation cohorts because if a predictor is difficult to obtain in practice, then the model including it may not be of clinical relevance. In the event of missing data, multiple imputation by chained equations (MICE)[14] will be used to impute missing values in order to avoid bias and make best use of the data, by replacing missing values with plausible values based on the distribution of the observed data. 10 imputed datasets will be created separately for each cohort.

17.1.1 Model development

Candidate predictor variables will be selected from those listed in the Table above. Their selection has been informed by subject knowledge using literature review and expert judgement. As predictor distributions should be wide to facilitate reliable predictions, we will explore the distribution of each predictor prior to selection. Relationships between predictors will also be investigated; where indicated we will group related variables into a composite variable or exclude if highly correlated with other variables. Candidate predictors will not be selected based on univariable analyses; this practice is discouraged because predictors that may be important in a multivariable model can be missed and may also lead to overoptimistic models. Therefore, all selected candidate predictor variables will be included in the multivariable logistic regression models without evaluations of association between outcome and predictor and assessment of statistical significance. To gain maximum diagnostic information, continuous variables will not be categorised. The linearity of continuous variables will be tested with restricted cubic splines. This may lead to the inclusion of non-linear terms in the models thus increasing the number of variables in the models. Overfitting, optimism, and miscalibration of the models will be addressed during model development by applying shrinkage using the least absolute shrinkage and selection operator (LASSO) method [15]. We chose this method because some regression coefficients may be shrunk to zero. Advantages of using shrinkage as part of our selection criteria of predictors include being able to drop variables with a coefficient of zero, and preventing

very extreme predictions. This allows models to be made as parsimonious as possible improving performance for a validation cohort.

17.1.2 Model validation and estimation of diagnostic accuracy

The predictive performance of each model will be assessed in terms of discrimination, that is the ability to distinguish between those who do or do not have a particular diagnosis, and calibration meaning agreement between predicted and observed probabilities. Discriminative ability will be assessed using the c-index. For a logistic model, this is equivalent to the area under the ROC curve (AUC). Bootstrap resampling will be used to calculate 95% confidence intervals for the c-statistic. From the qualitative research we will ascertain distributions of probability (risk) thresholds for clinical usefulness of the prediction in guiding treatment of each condition. The sensitivity and specificity for these risk thresholds will be plotted on an ROC plot for each model and confidence intervals computed. Calibration will be evaluated in two ways. Within each quintile or decile of predicted probability (depending on the distribution of data), the average predicted probability will be compared with the corresponding observed proportions. Calibration plots of average observed probability against predicted probability will be used to visually assess calibration. We will also quantify calibration by estimating the calibration slope of the prognostic index (linear predictor) using logistic regression with the linear predictor as the covariate. The value for the calibration slope should ideally be one signifying perfect agreement between the predicted probabilities and the observed probabilities. A calibration slope < 1 indicates that a model over-predicts while a calibration slope > 1 indicates under prediction.

17.2 Qualitative analysis

Interviews will be audio-recorded and transcribed, and transcribed data entered into qualitative analysis software. Clinician and patient interview data will be analysed separately. Due to the expected homogeneity of data resulting from the semi-structured interviews, we will use Framework Analysis to identify key themes (codes) emerging from the data, including those relating to usability and acceptability. The matrix output will allow us to compare themes across cases (patient/clinician) and within individual cases. We will assess the point of data saturation by continual review of interview transcripts.

17.3 Cost effectiveness analysis

The study will highlight all potential changes to routine care where cost savings/expenditures will occur, and therefore aid the determination of all cost parameters and health related outcomes which must be considered in any future cost-effectiveness analysis.

For the purposes of this work, a simple cost comparison will be performed with any relevant data routinely collected or made available throughout the study. Where economic data is not readily available, data will be sought from published resources, or estimated expert opinion. This will allow an early indication of the potential cost implications of the routine use of the clinical decision aid and, importantly, will inform planning for future clinical evaluations and cost-effectiveness analysis.

17.4 Other Analyses

17.4.1 Referral rates

The potential impact of the decision aid on referral rates will be calculated by expressing the difference between rates occurring during GP practice participation in the PriMUS study including consideration of urodynamic diagnoses provided by use of the reference test with the historical control of practices participating in the CPRD data collection.

18 Data Management

18.1 Source data

The source data for PriMUS study will be from a variety of sources. Data will be collected using an electronic system with paper CRF back up. There will also be data collected from participant's medical notes and patient reported questionnaires. Source data from flowmeters and urodynamic assessments will recorded, downloaded and stored electronically in individual patient folders within the database.

Training for completion of study CRFs will be provided to the appropriate study staff prior to study commencement at site initiation.

18.2 Completion of CRFs

All assessments and data collection will be completed using web-based CRFs. This is a secure encrypted system accessed by username and password, and complies with Data Protection Act standards. In the event that the web-based system is not accessible, paper CRFs will be used to record data. The data will then be inputted into the web-based system once it is accessible. A full data management plan will accompany this protocol and will be stored in the TMF.

18.3 Electronic CRFs

We intend to develop data recording for this study as a web-based system. This is a secure encrypted system accessed by an institutional password, and complies with Data Protection Act standards.
A user password will be supplied to investigators upon completion of all processes required prior to opening.

18.4 Paper CRFs

If the electronic database is not available, paper CRFs will be used and data will be entered on to the database at a later point. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.

CRF pages and data received by the CTR from participating study sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to respond to the data query on the data clarification form. The case report form pages should not be altered. All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the CTR and a copy retained at the site along with the participants' CRFs. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner. Further details of data management procedures can be found in the Data Management Plan.

18.5 Qualitative study data management

All the information, including any personal information (e.g. patient name), will be kept completely confidential. Recordings will not be labelled with patient name. Any written report of the research will have the patient's name removed. Written quotes of what the patient says in the interview may be used word for word, but quotes will be anonymised. Patient names will not appear on any publications. All study related records will be stored for 15 years. The results are likely to be published in medical journals over the next few years. The patient will not be personally identified in any report or publication. Full details of data management will be specified in the Data Management Plan.

19 Protocol/GCP Non-Compliance

The PI / local researcher should report any non-compliance to the study protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it. The CTR will assess the nature and severity of any issues of non-compliance in accordance with their SOPs.

20 End of Study definition

The end of the study is defined as the date of final data capture to meet the study endpoints. Sponsor must notify REC of the end of a clinical study within 90 days of its completion or within 15 days if the study is terminated early.

21 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the study shall not be destroyed without permission from the Sponsor.

22 Regulatory Considerations

22.1 Ethical and governance approval

This Study Protocol has been submitted to a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority (UKECA) for review and approval. A favourable ethical opinion will be obtained from the REC before commencement of any study procedures (including recruitment of participants).

This Study Protocol will be submitted through the relevant permission system for global governance via Health and Care Research Wales (HCRW) Permissions Coordinating Unit (PCU).

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

All substantial protocol amendments must be approved by the REC responsible for the study, in addition to approval by NHS Research and Development (R&D). Minor amendments will not require prior approval by the REC.

If the study is stopped due to adverse events or an urgent safety measure it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 calendar days of study closure. In the event of the study being prematurely terminated a report will be submitted to the REC responsible for the study within 15 calendar days.

A summary of the results will be submitted to the REC responsible for the study within one year of completion of study closure.

22.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the Data Protection Act 1998. The data custodian and the translational sample custodian for this study is the Chief Investigator(s).

Participants will always be identified using their unique study identification number and any additional identifiers. This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), name and postcode to register and trace participants with the HSCIC.

22.2.1 Data sharing plan

Data will be collected in a suitable format to facilitate sharing when required. This will be possible via Managed Access. We will also have a data sharing agreement in place with Birmingham University who are responsible for the statistical analysis.

22.3 Indemnity

As the research is sponsored by Cardiff University and carried out on NHS sites, the following statements will be appropriate:

- Non-negligent harm: This study is an academic, investigator-led and designed study, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical study and

they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this study. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Study (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

22.4 Study sponsorship

Cardiff University will act as Sponsor for study. Delegated responsibilities will be assigned to the sites taking part in this study.

The Sponsor shall be responsible for ensuring that the study is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005).
- The Data Protection Act 1998.
- Other regulatory requirements as appropriate.

The Sponsor has/will be delegating certain responsibilities to CTR, the CIs, PIs, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

22.5 Funding

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (project number 15/40/05) and will be published in full in Health Technology Assessment. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

High street vouchers to a maximum value of £40 will be offered to participants as a token of appreciation for their time in taking part in the study, this will cover any travel expenses incurred as a result of participating in the study.

The study will be adopted on the NIHR portfolio.

23 Study Management

23.1 Project Team (PT)

The Project Team (PT) will meet fortnightly and will include the Co-Chief Investigators, Study Manager, Data Manager, Statistician, Administrator and other research staff directly employed to the study. The project team will discuss all day-to-day management issues and will refer any key management decisions to the Study Management Group (SMG).

23.2 Study Management Group (SMG)

The SMG will consist of the CIs, Co-Applicants, Collaborators, SM, DM, SS and SA. The role of the SMG will be to help set up the study by providing specialist advice, input to and comment on study procedures and documents (information sheets, Protocol, etc.). They will also advise on the promotion and running of the study and deal with any issues that arise. The group will normally meet monthly throughout the course of the study. SMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

23.3 Study Steering Committee (SSC)

A Study Steering Committee (SSC), consisting of an independent chair, and three other independent members including a patient representative, will meet at least annually. The first meeting will be before the study commences to review the Protocol and arrange the timelines for the subsequent meetings. If necessary, additional/more frequent meetings may occur. The TM and TS will attend as observers. The SSC will provide overall supervision for the study and provide advice through its independent chair. The ultimate decision for the continuation of the study lies with the SSC. SSC members will be required to sign up to the remit and conditions as set out in the SSC Charter.

23.4 Public and Patient Involvement (PPI)

VOICE North, a public engagement and involvement body – primarily for older service users, have indicated strong support to participate in the study as PPI contributors. Mrs Tracy Scott (Patient, Carer and Public Involvement manager, Newcastle upon Tyne Hospitals Trust Foundation) has agreed to act as the co-applicant for the study, and she will be supported by Dr Alison Bray.

We plan to raise awareness of the study and the need to improve management of male LUTS nationally via bi-annual events held in the North East of England and Wales coordinated by the Cystitis and Overactive Bladder Foundation (COB) (soon to be rebranded as UK Bladder Health Foundation).

In addition, we will also convene regional PPI representatives from COB/UK Bladder Health website /VOICE North/ Involving People / INVOLVE and (early) recruited patients in the study, to provide group feedback. We will ensure our public contributors have equal opportunity to manage and influence our study, and with support help us to take strategic and specific decisions within and across the project phases. A particular area for advice will be the production of patient information sheets, concerning the range of investigations to which participants are asked to consent for the study.

We will appoint PPI representatives to our Study Management Group and Independent Steering Committee.

PPI contributors will also join subgroups to: plan data collection; review early findings; plan the consensus / stakeholder events; lead the public strand of our dissemination activities. We will support public contributors in line with good practice and our (Trials Unit & PRIME Centre Wales) Standard Operating Procedure, provide honorariums and access to training, cover all expenses, and ensure the content and location of meetings are accessible.

24 Quality Control and Assurance

24.1 Risk Assessment

A Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment includes:

- The known and potential risks and benefits to participants
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This study has been categorised as low risk, where the level of risk is no higher than the risk of standard medical care. A copy of the study risk assessment may be requested from the Study Manager. The study risk assessment is used to determine the intensity and focus of monitoring activity (see section 24.2).

24.2 Monitoring

The risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the PRIMUS study. Low/Low+ monitoring levels will be employed and are fully documented in the study monitoring plan. Investigators should agree to allow study related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

24.3 Audits & inspections

The study is participant to inspection by the Health Technology Assessment programme (HTA) as the funding organisation. The study may also be participant to inspection and audit by Cardiff University under their remit as Sponsor.

25 Publication policy

All publications and presentations relating to the study will be authorised by the SMG and will be in accordance with the study's publication policy. In addition to the required final report and monograph for the HTA Programme, we will publish the main study results in international peer-reviewed journals and present at national and international scientific meetings. With the assistance of our collaborators and lay representatives we will disseminate the study findings to a wide NHS and general audience and vigorously promote uptake of the study results into clinical care. This will include presentations at meetings and written executive summaries for key stakeholder groups such as Primary Care Trusts, Secondary Care Trusts, Health Boards, Royal Colleges, Medical Schools, and relevant patient groups.

26 Milestones

Month 1-6 = Study Set Up

Month 7-12 = Patient Recruitment and Follow Up (including 6 month Pilot and Acceptability Phase)

Month 19-24 = Results and Analysis

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