Overactive bladder (OAB) syndrome is often described as urgency that occurs with or without incontinence and usually with frequency and nocturia. In a UK study, OAB symptoms were found in 12% of the general population. In individuals over 40 years of age, 34% report significant lower urinary tract symptoms. Detrusor Overactivity (DO) is an observation characterised by involuntary bladder muscle contractions (spontaneous or provoked) associated with urgency during the filling phase of the bladder test called urodynamics (UDS). Urinary symptoms alone can be unreliable in establishing the diagnosis of DO at initial presentation, so some practitioners recommend UDS. The patient with this condition can be treated with a combination of antimuscarinic medications and bladder training in the first instance. UDS is invasive, poorly tolerated by patients and costly investigation (£212 per procedure, NHS reference cost, 2008) with associated risk of urinary infections. Bladder ultrasound (BUS), on the other hand, costs £140 per procedure and is relatively non invasive.

There have been guidelines from the National Institute for Health and Clinical Excellence (NICE) and a UK Health Technology Assessment report on this subject in 2006. Both the documents have highlighted the scale of the problem, the burden on the NHS, and the dearth of evidence. A specific recommendation was for further research into diagnostic technologies used for assessing urinary incontinence, particularly the role of ultrasound. The NICE guideline (CG40), in its section on Imaging, states: “Further studies are required to clarify the role of ultrasound for the assessment of overactive bladder.” The reports found there were substantial variations in the quality of the existing studies, methods of performing the BUS and UDS, thresholds for defining presence of disease and the format in which the findings were reported.
Our study is designed to address this specific question. If accurate and cost-effective, BUS will be able to reduce the need for UDS.

The BUS Study aims:

1. To estimate the accuracy of BUS in the diagnosis of DO; the purpose of this is to see whether BUS has sufficient accuracy to replace UDS in the diagnosis of DO.
2. To investigate the value added by BUS to information already obtained from routinely used initial non-invasive tests (history, bladder diary, disease specific quality of life (QoL) questionnaire).
3. To conduct a decision-analytical model based economic evaluation comparing the cost-effectiveness of various care pathways (including pathways that incorporate BUS).

All women presenting with frequency, urgency symptoms at the participating centres will be invited to participate in this study that aims to recruit 600 women over 24 months for the assessment of test accuracy. For the index test (BUS), we will measure bladder wall thickness from transvaginal ultrasound scans, which will be a continuous variable reported in millimetres. For reference standard, UDS will be performed on all patients for DO verification. Other variables and results of routinely performed tests will also be obtained, and will be used for evaluation of the add-on value of BUS.

The main analysis for diagnostic accuracy will estimate sensitivity, specificity, predictive values, likelihood ratios and their confidence intervals. Using multivariable logistic regression analysis, predictive probabilities for various combinations of history, bladder diary and disease specific QoL questionnaire will be generated. Health economic evaluation will be performed to establish the relative cost-effectiveness of BUS alone and in combination with existing tests.
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Protocol Versions
1.0 Submitted to Nottingham REC 2
1.1 Version resubmitted to Nottingham REC 2
1.2 Version approved by Nottingham REC 2
2.0 Version approved by Nottingham REC 2
3.0 Version approved by Nottingham REC 2
4.0 Version approved by Nottingham REC 2
5.0 Version approved by Nottingham REC 2

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The University of Birmingham is the principal sponsor and the Birmingham Women’s NHS Foundation Trust is the co-sponsor. Dr Pallavi Latthe, Consultant Urogynaecologist, is the Chief Investigator.

The University of Birmingham is responsible for the design of the protocol, obtaining necessary approvals, for the management and analysis of the study. Birmingham Women’s NHS Foundation Trust is responsible for the Chief Investigator and for safety monitoring. The Study Management Committee is jointly responsible for overseeing good clinical practice and the Investigators are responsible for obtaining informed consent and care of the participants.
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1. BACKGROUND

1.1. Clinical Context

The International Continence Society (ICS) has standardised terminology for classification of urinary incontinence (UI-the complaint of any involuntary urinary leakage). (1) Urge urinary incontinence is involuntary urine leakage accompanied or immediately preceded by urgency (a sudden compelling desire to urinate that is difficult to defer) and mixed urinary incontinence is involuntary urine leakage associated with both urgency and stress (exertion, effort, sneezing or coughing). Overactive bladder (OAB) syndrome is often described as urgency that occurs with or without incontinence and usually with frequency and nocturia. In a UK study, OAB symptoms were found in 12% of the general population. In individuals over 40 years of age, 34% report significant lower urinary tract symptoms. (2) Detrusor Overactivity (DO) is an urodynamic observation characterised by involuntary detrusor contractions (spontaneous or provoked) associated with urgency during the filling phase of UDS. (1)

Incontinence seriously influences the physical, psychological and social wellbeing of affected individuals. (3) The impact on the families and carers of women with incontinence is profound, and the resource implications for the NHS considerable. (4) Urinary symptoms alone can be unreliable in establishing the diagnosis of DO at initial presentation; (5) so some practitioners recommend urodynamic testing. Urodynamics (UDS) is invasive, poorly tolerated by patients, and costly investigation (£212 per procedure, NHS reference cost, 2008) with associated risk of urinary infections. Bladder ultrasound (BUS), the index test we will evaluate, costs £140 per procedure.

There has been a NICE guideline and a HTA report on this subject in 2006. (6;7) Both the documents have highlighted the scale of the problem, the burden on the NHS, and the dearth of evidence. A specific recommendation was for further research into diagnostic technologies used for assessing urinary incontinence, particularly the role of ultrasound. The NICE guideline (CG40), (6) in its section on Imaging, states: “Further studies are required to clarify the role of ultrasound for the assessment of overactive bladder.” Our study is designed to address this specific question. If accurate and cost-effective, BUS will be able to reduce the need for UDS.

1.2. Evidence for the Accuracy of Bladder Ultrasound as a test for diagnosing Detrusor Overactivity

We performed a systematic review of test accuracy studies that reported data on women who had an ultrasound scan to measure bladder wall thickness (BWT) against the reference standard of UDS to confirm DO. (8)

Search strategy

Electronic searches were conducted in Medline, EMBASE, LILACS and CINAHL from database inception to 2008. The reference lists of known relevant papers were searched for any further articles.

Methods

Two reviewers independently selected articles without language restrictions, and extracted data covering study characteristics, study quality and results. We computed or extracted sensitivity and specificity with 95% confidence interval for individual studies. Pooling these results in meta-analysis was inappropriate due to heterogeneity and lack of data to allow for the construction of 2x2 tables.
**Summary of Results**

- Five studies, 3 prospective and 2 retrospective, including 1556 women were identified.
- There were substantial variations in the quality of the studies, methods of performing the BUS and UDS, thresholds for defining presence of disease and the format in which the findings were reported.
- Four studies showed that BUS had discriminatory properties to diagnose DO, although the reported performance varied amongst the studies. Increased BWT was found more in women with DO than those with other types of incontinence. Using 5 mm cut off, the point estimates of sensitivity reported varied from 40-84% and specificity from 78-89%.
- Only one retrospective study reported on the test-retest reliability with an intraclass correlation co-efficient of 0.82 (95% CI 0.63-0.91).
- None of the studies evaluated acceptability of BUS testing to patients or cost effectiveness data.

**Table 1 The accuracy of BUS for diagnosing DO**

<table>
<thead>
<tr>
<th>Study, date, country, design</th>
<th>Population</th>
<th>Test</th>
<th>Reference Standard</th>
<th>Mean (+/- 2SD or 95% confidence interval) amongst those with and without DO in mm/Specificity &amp; sensitivity % at cut off&gt; 5mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lekskulchai et al 2008 (9)</td>
<td>686 women (largely Caucasian) who attended a tertiary UDS service, who underwent a full multichannel UDS and translabial ultrasound, between Nov 02-Jan 06</td>
<td>After bladder emptying using translabial ultrasound (USS) - the iso-to hypoechoic layer at the bladder dome opposite the internal urethral meatus within 2 cm of the midsagittal plane. Three separate measurements were made and the mean was taken.</td>
<td>Multi-channel UDS confirmed to ICS standards using Uromac Acquidata, Neomedix, Australia</td>
<td>4.7 +/- 1.9 in DO vs. 4.1 ± 1.6 The Receiver Operator Curve analysis revealed an area under curve of 0.606 (0.56-0.65)</td>
</tr>
<tr>
<td>Minardi et al 2007 (10) Italy Prospective</td>
<td>66 patients referred to the outpatient clinic for stress and urge urinary incontinence (14 controls also studied)</td>
<td>Measurement of thickness at bladder dome within a maximum interval of 1 week after UDS using 3.5 MHz probe for translabial approach and 6.5 MHz for the introital approach</td>
<td>UDS using Duet multi-P Medtronic according to ICS criteria</td>
<td>7.1 +/-1.6 in DO 3.9 +/-1.9 in controls 4.1 +/-1.1 in USI (P=0.019)</td>
</tr>
<tr>
<td>Yang et al 2003 (11) Taiwan Retrospective</td>
<td>492 patients with lower urinary tract (LUT) symptoms who had undergone UDS and USS of the LUT and who had normal urinalysis findings, negative urine culture results, or both.</td>
<td>Measurement of bladder wall thickness using transvaginal ultrasound (TV USS) cystourethography</td>
<td>UDS performed on Medical Measurement Systems UD-2000 multichannel recorder at a filling rate of 80 ml/min with patient sitting upright in a birthing chair.</td>
<td>5.5 (5-6.6) in DO 5.6-6.4 mm in USI 5-6.2mm in mixed incontinence</td>
</tr>
</tbody>
</table>
Robinson et al 2002 (12) UK Prospective
128 women referred for ambulatory UDS with equivocal laboratory UDS or whose symptoms were not explained by the laboratory UDS findings. 1/128 woman had voiding difficulties and hence was excluded from the study.

Measurement of BWT using TV USS
Ambulatory urodynamics-DO diagnosed if detrusor pressure rise was recorded in association with symptoms of urgency and/or urge incontinence.

6.7 (6-7.4) in DO
5.1mm (4.6-5.6) in normal
4.8 mm (4.4-5.3) in Urodynamic Stress Incontinence

Khullar et al 1996 (13) UK Prospective
184 patients attending clinic for laboratory UDS due to urinary symptoms and who consented to participate in the study.

BWT after emptying bladder at TV USS using a 5MHz probe and postmicturition residual was checked to ensure <50 mls. The measurements were made at maximum magnification in 3 places: 1. perpendicular to the luminal surface at the thickest part of the trigone, 2. at the dome and 3. at the anterior wall
Mean BWT = dome+ anterior wall+ trigone/3

Video UDS per ICS standard in supine position using 100ml/min filling rate. Various provocative tests were used. BUS <3.5mm or with >5mm BUS but no DO went onto have ambulatory UDS on a separate day which lasted 4 hours.

89 (78.8- 96.11)% specificity
84 (75.8 - 89.7)% sensitivity

1.3. Objectives of the BUS Study

1. To estimate the accuracy of BUS in the diagnosis of DO; the purpose of this is to see whether BUS has sufficient accuracy to replace UDS in the diagnosis of DO.

2. To investigate the value added by BUS to information already obtained from routinely used initial non-invasive tests (history, bladder diary, disease specific quality of life (QoL) questionnaire).

3. To conduct a decision-analytical model based economic evaluation comparing the cost-effectiveness of various care pathways (including pathways that incorporate BUS).

4. To assess the acceptability of BUS to women and to health care professionals

2. STUDY DESIGN

2.1. Overview of test accuracy studies

A test accuracy study is different to an effectiveness study in that randomisation of subjects is not involved. It is designed to generate a comparison of measurements obtained by index tests with those obtained by reference standards. In this way the accuracy of index tests can be estimated. A reference standard is a test that confirms or refutes the presence or absence of disease beyond reasonable doubt sometimes also known as the gold standard. Ideally, all participants must have results from both the index test and the reference standard. Bladder wall thickness by ultrasound (BUS) is the index
test whereas the reference standard will be the identification of Detrusor Overactivity (DO) by urodynamics (UDS).

There are many possible sources of bias in accuracy studies (14) and these have recently been highlighted in the STARD statement. (15) Selection bias may arise if the sample is not suitably representative of the population. This is likely to occur with use of non-consecutive or convenience sampling. The study will seek to recruit all consecutive eligible women. A related issue is that of spectrum bias whereby the accuracy of tests varies among study samples with differences in disease severity (a measurable characteristic). Sensitivity analysis will explore the variation in test accuracy due to spectrum composition. Age, menopausal status, body mass index, duration and type of symptoms, duration of antimuscarinics use etc. would be some of the variables that we would look at for sensitivity analysis.

Empirical studies have shown that studies with differential verification produce more biased estimates of accuracy than studies with complete verification by the preferred reference standard, particularly when differential verification is not pre-specified in the design or completely at random. The direction and magnitude of bias is likely to depend on whether differential verification will lead to different detection rates of DO under different reference standards. We are avoiding this by using a complete verification design.

2.2. Brief summary

The study will evaluate the accuracy of BUS in making a diagnosis of DO using laboratory multichannel urodynamics (UDS) as the reference standard. An outline of the test accuracy study is shown in Figure 1. For the index test (BUS), we will measure bladder wall thickness from transvaginal ultrasound scans, which will be a continuous variable reported in millimetres. For reference standard, UDS will be performed on all patients for DO verification. Other variables and results of routinely performed tests will also be obtained, and will be used for evaluation of the add-on value of BUS. Health economic evaluation will be performed to establish the relative cost-effectiveness of BUS alone and in combination with existing tests.
2.3. Large, simple study: minimal extra workload

In order to obtain the large number of patients necessary for the reliable evaluation of the BUS test, the study will need the participation of more than one centre. To make these practicable, study procedures need to be kept simple, with the minimal extra workload placed on participating clinicians, beyond that required to manage their patients. This will be achieved by simple entry procedures, early consent of women, the use of standard local testing regimens, minimising documentation and streamlining data collection procedures. Regular newsletters will keep collaborators informed of study progress, and regular meetings will be held to report progress of the study and to address any problems encountered in the conduct of the study.

2.4. Setting

The study will be carried out in 22 units in the UK. These units serve a large, socio-economically and ethnically diverse population, which will aid generalisability of findings. The units also represent the spectrum of settings, from a community clinic to busy district general hospital to a specialised tertiary referral centre.

3. ELIGIBILITY

The following inclusion / exclusion criteria will be used:

3.1. Inclusion criteria

- Frequency of 9 or more voids in 24 hours as reported in the 3 day bladder diary at least on one of the days
- Mild – severe urgency (cannot defer the urge to void) on at least two occasion in 3 day bladder diary
- Post void residual volume <100 mls on screening
- Written informed consent

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Figure 1 Flow chart of study organisation
• If patient has had previous stress incontinence surgery &/or Botox, it was >6 months ago

3.2. Exclusion criteria

• Pregnancy and up to 6 weeks postpartum.
• Pure symptoms of stress incontinence or stress predominant mixed incontinence
• Evidence of cystitis (dipstick positive for leucocytes/nitrites)
• Voiding difficulties (post void residual >100 ml)
• Prolapse > grade II (any compartment)
• Urodynamics, assessment in the past 6 months
• Use of antimuscarinics for more than 6 months continuously.
• Current use of anti-muscarinics (e.g. Tolterodine, solifenacin, oxybutynin). If the woman is taking anti-muscarinics at the point of consent, she will be eligible if:
  o Medication is ceased immediately
  o There is a delay of at least 2 weeks until the index and reference tests are carried out.

3.3. Recruitment of participants and consent

Ideally consent is sought under unhurried circumstances, when entry criteria are fulfilled. Consent will be sought in stages:

• A patient information leaflet will be sent to all women who are referred with frequency and urgency to the participating clinics along with their appointment letters to attend urogynaecology, urology or urodynamics clinics. This leaflet will be available in different local languages to reflect the ethnic communities at each centre.

• A copy of the information leaflet will be also given out to women who present primarily with prolapse but have frequency and urgency symptoms. Any patient declining participation will have this recorded in the outpatient notes and centres will be asked to keep a log of women screened for the study with information regarding their eligibility and participation. This will be monitored and reported on to TSC DMC as appropriate.

• The consent form can be signed by the woman at the first appointment if she wishes to do so. To provide enough time for consideration and to provide opportunities to ask questions, consent will be reconfirmed verbally at the next appointment when testing is undertaken.

• Women will also be asked to consent to their GP being informed of their participation in BUS, and to allow the study team to contact their GP should they need to trace the participant. Participating Centres are reminded that it is Good Clinical Practice to photocopy this GP letter and put a copy in the patient’s notes.

Wherever necessary, appropriate interpreters will be asked to aid discussion relating to study participation. It is anticipated that acceptability of the test and willingness to participate in the study may potentially vary between ethnic groups. We will record anonymous baseline demographic and ethnicity information from all women invited to take part, including those who decline to take part, or those who are later identified as ineligible. We will collect patient’s age, parity, ethnicity and language. These details will be stored anonymously. This will establish the take-up rate of the study.

All urogynaecology nurses and junior doctors will receive training regarding the introduction of information about the study and instruction on their roles from the local coordinating clinicians. This will occur during team meetings and the information provided
will be reinforced periodically throughout the study by further meetings and newsletters from the Study Office.

3.4. Organisation of Recruitment

Recruitment will be organised and supported by dedicated clinical principal investigators. Documentation will be provided by the BUS Study Office and the clinical research fellow will be available to support clinics in some centres local to Birmingham. We believe that that the following strategy is likely to be successful in achieving maximum recruitment.

- Appointment or nomination of a dedicated nurse at each centre with responsibility for identifying eligible patients, overseeing preliminary consent in the clinic of her centre, data collection and problem resolution. Resources for this post may be available from the Trust’s R&D support allocation or via the local comprehensive research network. (see Section 8.7)

- Appointment of a clinical research fellow, based at Birmingham Women’s Hospital, who will liaise with all the local principal investigators at each centre, provide training (USS) and trouble-shoot recruitment and testing problems.

- Provision of simple written study information, supported by face to face discussion with urogynaecologists and continence nurses.

- Provision of regular feedback on progress in study recruitment, including individual hospital teams’ performance and progress against targets.

- Regular newsletters to all relevant staff involved in the study.

4. TESTS AND PROCEDURES

4.1. The index test

4.1.1 Development of the index test

It is essential to explore the technical and practical aspects of conducting the bladder wall thickness test before the commencement of the accuracy study. A technical feasibility study will be carried out to establish the most practicable methods of testing and reporting results in the outpatient setting. This will also allow the development of programmes for quality assurance and for training staff to perform bladder wall thickness. This will be one of the roles of the research fellow.

We recommend use of an Ultrasound machine capable of producing high-quality images with simplified controls and a suitable range of transducers including a transvaginal transducer with 7-9 MHz being optimal, but with a frequency no lower than 5 MHz. We will use a portable machine at Birmingham Women’s Hospital, so it could also be taken to community clinics to facilitate on-site scanning. For the other centres involved in the study, respective radiologists and clinicians will be consulted as to the best way forward for performing this test in terms of machine, rooms and who would perform the scan (radiologist, urogynaecologist, sonographer or nurse). The type of ultrasound machine and transducer used at each site will be collected at the start of the study and local principal investigators will be required to notify the Study Office of any change or upgrade to their ultrasound machines.

The date and time of testing will also be recorded. We intend to assess whether it has “high reproducibility” by doing interobserver reliability measurement. This will be done by the radiologist or urogynaecologist (blinded to the result) who will repeat measurements on 20% of the stored scan images for each centre.
4.1.2 The index test: bladder ultrasound

At the centres where ultrasound will be undertaken in the urodynamics suite, the BUS will be performed prior to filling cystometry stage of UDS by an independent observer, but at the same clinic visit, avoiding the bias that arises from delay in verification. The scans will be performed via the transvaginal approach on empty bladder as this is well tolerated by most patients and should require minimal training. In patients in whom the transvaginal approach would not be feasible, a translabial approach would be used. It should take no more than 10 minutes to perform the scan. It is preferable to get all measurements on a single image where possible.

Bladder wall thickness will be measured at 3 sites in millimetres using tools provided on the ultrasound machine: perpendicular to the luminal surface of the bladder at the thickest part of the trigone, at the dome of the bladder in the midline, and at the anterior wall of the bladder also in the midline (as well as the detrusor thickness at the dome in midline and 1 cm on either side of the midline). Bladder volume will also be assessed and recorded at the same time as sometimes patient might have voiding difficulties and this variable will be taken into account during analysis. If they have a PVR >30 ml, the PVR and BWT will be assessed after double voiding. If the patient has a PVR >100ml inspite of double voiding, that patient will be excluded from the study.

At centres, where the BUS will be done in the radiology department, the urodynamics will be carried out blinded to the ultrasound result, within 4 weeks of the BUS. If this 4 week cut-off period is breached, there is a further 4 week window in which the second test data should still be collected, but this will be classed as a protocol violation. Whilst UDS cannot be blinded to the history of the patient (as it is designed to reproduce the patient’s symptoms), the BUS will be blinded to the history of the patient, and both UDS and BUS results will be blinded to each other.
4.1.3 Additional tests and information

We aim to collect a minimal demographic and clinical dataset including age, ethnicity, parity and significant medical/surgical history, pad usage and costs etc. We aim to use the NHS number as the primary identifier and to track individuals throughout the NHS.

Clinical history

The ICIQ-OAB(16) will be administered at baseline when the patient consents to participate in the study and at 6 months. The EPAQ questionnaire may also be accessed at some participating research centres.

Bladder diary

The patient starts recording on the sheet each day when she gets up in the morning for 24 hours including the waking up and bedtime. The patient is asked to record the type and amount of fluid intake, the times and volumes of urine voided, how often she leaked and what she thought caused the accident as well as symptoms like urgency and amount of leakage. Women will be encouraged to complete a minimum of 3 days of the diary covering variations in their usual activities, such as both working and leisure days.(6) This can be done anytime between receiving letter of appointment till day before clinic attendance.

Urine dipstick

This will be performed to rule out presence of nitrites, leucocytes and blood prior to UDS as is done in current clinical practice.

Quality of life

We will also administer EuroQoL EQ-5D and ICECAP-A at baseline and 6 months. As a reward for returning completed questionnaires, patients will be offered the opportunity to be entered into a prize draw for Boots vouchers.

While the former is a widely used measure of quality of life, the latter is a recently developed measure of capability for use in the adult population with general population values providing an index score. The Health Economics Unit at the University of Birmingham is supported by the NIHR and has been given the specific methodological remit to explore capability and well being of the adult population using ICECAP. (30)

4.2. The reference standard: urodynamics

UDS is a term used to describe a combination of tests that look at the ability of the bladder to store and expel urine. The UDS will consist of uroflowmetry, pressure recording during filling phase, and combined pressure flow studies. This will be performed in a standardised manner as per the Good Urodynamic Practice guidelines from the International Continence Society(17) and a Standard Operating Procedure which has been produced for the study based on this. It will be performed without the influence of antimuscarinic drugs, with patients being asked to stop these drugs for 2 weeks before testing. We will record information on duration of use of these drugs, prior continence surgery. The patient will be asked to arrive with a comfortably full bladder. After counselling and providing consent for the test, they will void on an uroflowmeter, in the sitting position to assess the voiding function. Following this, catheters will be inserted in the bladder and vagina/rectum. (18) The residual urine volume will be recorded. The bladder will be filled with room temperature normal saline with or without contrast medium at 100ml/min in sitting position and patient will be asked to cough every minute to check for adequate subtraction. The patient will be asked to report the first, normal and strong desire to void, if she gets symptoms of urgency, pain or if she leaks. The filling will be stopped at 500
millilitres or when the patient has strong desire to void. The filling catheter will be removed and various provocation tests like running the tap, coughing, and exercise will be carried out. At the end of the test, the patient will be asked to cough and then sit on the toilet and void in privacy. The diagnosis of DO is made when there is phasic or terminal detrusor contraction detected on the trace with or without urgency (either spontaneous or provoked by running taps, coughing etc.). The other diagnoses would include urodynamic stress incontinence (USI), mixed DO and USI, low compliance, voiding dysfunction or normal urodynamics.

We plan to offer ambulatory UDS to women who are negative on laboratory urodynamics for DO at the Birmingham Women’s Hospital. This will enable us to assess the additional positive rate on adding ambulatory urodynamics. This should be undertaken within 12 weeks of the standard UDS, and patient’s acceptability of the ambulatory test assessed separately to that of the standard test

4.3. Compliance and follow-up issues

In the systematic review of BUS as a diagnostic tool, none of the studies reported specific problems about non-compliance, i.e. declining participation after having given consent to take part. The key issue for us is the timing of the index test and the reference standard to avoid loss of participation after consent has been obtained and to reduce the impact of variation in result with time. We have designed the study to tackle this issue by performing the index test and the reference standard at the same appointment wherever possible or within a maximum of four weeks. Ideally patients should be registered on to the study at the time of their first test (otherwise there should be no more than 6 months between registration and testing).

4.4. Quality Control

Quality assurance of testing will begin with a clearly documented staff training programme. A register of staff who have been trained, and their competence assessed will be maintained, and only staff whose names appear on this list will be permitted to undertake testing. Staff will also receive regular update training and periodic reassessment of their competence by assessing interobserver variations.

Two SOPs will be in place: one outlining procedures for performing the ultrasound; the second for ensuring competence is achieved before commencing recruitment. A training DVD will be made available to all those performing the test. The clinician doing the ultrasound will be asked to send electronic images as specified in the SOP (or if this is not possible a print-out) of each PVR/BWT test they perform, one before the callipers are placed on the bladder image and one after they have set the callipers. The images will be anonymised before adding to the study database and then 20% from each centre will be reviewed for the accuracy of both probe placement and calliper placement. The name of the clinician performing the scan and the patient’s hospital will remain blinded to the reviewer. We also intend to review UDS traces for inter-observer reliability. Towards this end, we will ask for a copy of the UDS trace of patients recruited at a centre until the team is satisfied.

Any violations to the protocol will be monitored by the use of site visits, where a sample of patient notes will be checked against the case report forms.

4.5. Serious and unexpected adverse events

There are no foreseeable risks of mortality or significant morbidity associated with testing. Every effort will be made to minimise any risk through training. All serious adverse
events believed to be associated with the study should be reported by fax to the Study Office as soon as possible. This report should be followed within 2 weeks by a completed SAE form. For the purposes of this study, “serious” adverse events are those occurring in the participants which are fatal, life-threatening, disabling or require some form of medical or surgical treatment, arising within two weeks from either the BUS or UDS tests.

4.6. Other management
All other aspects of patient management are entirely at the discretion of the local doctors who will follow the local guidelines for treatment. (19)

5. OUTCOME MEASURES
The BUS testing procedure will be standardised in the first phase of the study and criteria for interpretation have been determined a priori.

5.1. Accuracy measures
The first objective of the study is to determine the accuracy of BUS in the diagnosis of DO. To do this, the comparison of BUS against UDS will be made and estimates of sensitivity, specificity, predictive values, likelihood ratios and their 95% confidence intervals calculated.

The second objective was to investigate the value added by BUS to information already obtained from routinely used initial non-invasive tests (history, bladder diary, urine dipstick).

5.1.1. Assessment of patient acceptability
We define acceptability broadly in this study to incorporate the psychological impact of scanning on patients. We will examine acceptability of BUS scan and UDS in bladder problems to patients, using two structured questionnaires. The questionnaires have the same content, but one relates to experiences of the BUS scan and other to the experiences of the UDS. They have been designed specifically for the study incorporating standardised measures, and will be administered as soon as is practicable after testing to limit recall bias whilst being sensitive to the distress of patients. Otherwise, if appropriate, the questionnaires will be sent to the patient by post.

In designing the questionnaires it will be important to maximise the precision and validity of the instrument. As this is not a randomised-controlled trial, no comparison across testing procedures will be carried out where maximum differences in scores would be expected. Patients will also be asked whether they would be prepared to have BUS testing after future treatments, or recommend it to others, since these give the most reliable measures of satisfaction. In addition, comparisons will be made using all data across social, ethnic, age and parity groups to see if testing is acceptable across all groups and, if it is not, the areas where acceptability is low and negative impact is high, so that procedures may be reviewed.

5.1.1.1. Measuring Distress
Psychological distress will be assessed across the populations using standardised instruments, so that levels of distress can be compared to population norms and to levels measured in other diagnostic studies. Specifically we will use the short 6-item version of the State anxiety form of the Spielberger State-Trait Anxiety Inventory (STAI). This instrument has been widely used and validated in a number of clinical studies on
diagnostic testing (20). It is a short, closed format questionnaire of current anxiety levels, and forms part of the Test Acceptability Questionnaires.

5.1.1.2. **Assessment of acceptability to health professionals**
The acceptability of BUS as a routine procedure to health professionals will be addressed by holding focus groups with nurses and clinicians after they have had experience of this best. Issues to be explored will include perceptions of the efficacy of testing, costs to staff in terms of time and effort involved, perceived benefits of testing, professional views on the impact on patients. The discussions of the focus groups will be recorded, transcribed and analysed using interpretative phenomenological analysis.

5.2. **Health economic outcomes**

**Model Based Economic Evaluation**
The objective of the economic evaluation is to compare the relative cost effectiveness of adding BUS test alone or as an adjunct to current practice as well as various other possible care pathways, against the current and various other care pathways alone, in the diagnosis of DO.

2.11.1 **Perspective and data collection**

If BUS is shown to be effective, either alone or as adjunct to the standard practice of use of clinical history, then it is likely that important cost implications will be imposed on the health care sector. For example, BUS may indicate the need for additional testing with UDS compared to standard investigations which could increase the number and extent of subsequent tests and treatment with antimuscarinics etc required by the individual. Alternatively the costs associated with BUS and a more accurate diagnosis may lead to a reduction in costs associated with unnecessary or ineffective subsequent treatments. The economic evaluation will take the form of a cost-effectiveness analysis based on an outcome of cost per DO case detected and cost per UDS test avoided. The analysis will adopt the perspective of the NHS.

Therefore data collection required for the model based economic evaluation will include:

- The equipment, other resource use and costs associated with BUS and UDS. A time and motion study will be undertaken to establish resource use associated with BUS and UDS.
- Knock-on costs associated with further tests and treatments that are required as a result of the diagnosis
- Equipment, resource use and costs associated with current practice and other available treatment pathways
- Accuracy of the USS test and current practice package compared to the accuracy of current practice tests alone
- Effectiveness of alternative intervention pathways that are followed as a result of the diagnosis
- Outcomes such as quality of life associated with DO
Cost data will be collected from two principal sources. First, once the clinical evidence has been synthesised into the main strategies of diagnosis and treatment, relevant studies will be examined for their data on costs and resource use. These data will be subject to relevant quality criteria. Additional cost data will be available from other sources such as the National Schedule for Reference Costs. If necessary primary cost and resource data will be collected from the Birmingham Women’s Hospital to complete any gaps in the information required for the modelling process.

Additional literature searches will be undertaken to help populate the decision model. The clinical Chief Investigator will work in close liaison with the health economist to identify the model questions. Information to answer these questions will be provided by focused searching of appropriate databases, including reference cost databases, statistical sources and other sources of relevant information.

5.3. Data management and validation
5.3.1 Confidentiality of personal data
The study will collect personal data and sensitive information about the participating women. Participants will be informed about the transfer of this information to the BUS Study office at the University of Birmingham Clinical Trials Unit (BCTU) and will be asked to consent to this. Acceptability questionnaires will be pseudoanonymised by using study numbers and patient initials. Participant demographic data, test results and questionnaire answers will be stored on a secure server, inputted where possible via the internet using secure socket layer encryption technology. Remaining data will be returned by post to the BCTU. The use of the patient's NHS number will minimise the risk of disclosure of identifiable data. Only registered study personnel will have access to the database.

All participant data will be processed and stored according to the MRC guidelines of use of personal data. All personal information obtained for the study will be held securely and treated as confidential. All staff, at the hospitals, in the community or at the BCTU, share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published.

5.3.2 Long-term storage of data
All participant data will be stored on computer for 15 years after recruitment in accordance with MRC guidelines on the archiving of personal medical data for research.

6. ACCRUAL AND ANALYSIS
6.1. Sample size
The approach we have used in the sample size calculations is to consider the power that a study of a certain size has for the lower limits of the confidence intervals for both sensitivity and specificity to exceed particular values (and hence prove that the test is statistically significantly superior to those values).

The primary analysis will be to estimate test accuracy. A sample size of 600 sets of the two tests, presuming a prevalence of 50%, (14) will provide 300 women for the estimate of sensitivity and 300 for the estimate of specificity. This allows estimation of sensitivities and specificities with 95% confidence intervals of width 10% for sensitivity and specificity values between 70% and 95%, and narrower for higher values. This level of precision will be adequate to assess the usefulness of the test.
6.2. Projected accrual and attrition rates
Accrual and attrition rates will be closely monitored against our target, and in the unlikely event that recruitment is insufficient, the Study Management Group have identified other units likely to be able to participate.

6.3. Analysis for test accuracy study
The primary analysis will involve estimation of the test accuracy of BUS by calculating sensitivity, specificity, predictive values, likelihood ratios and their 95% confidence intervals. In the first instance average BWT at the 5mm threshold (13) will be used to dichotomise results, although accuracy estimates at various thresholds of BWT will be presented by means of a Receiver operator characteristics (ROC) curve; furthermore, BWT will be trichotomised to < 3mm, 3-5 mm and >5mm to provide multilevel likelihood ratios.

Secondary analyses
We will utilise the reference standard information obtained from UDS to compare clinical history with DO. From such a design it is possible to estimate the absolute sensitivity or specificity. It is also possible to estimate the trade-off between additional true positives and false positives related to the addition of BUS to the standard history taking.(22) The statistical significance of the difference will be assessed using McNemar’s test for paired data, and confidence intervals for the ratios computed using the methods of Cheng and Macalouso.(23) The same approach can be utilised for comparing BUS and clinical examination. To determine the added value of BUS over and above diagnostic information gained by other index tests (history, bladder diary, cough stress test, individually and combined) we will use multivariable modelling. The project will allow development of methodology for contribution of tests in differential diagnosis (DO vs. stress incontinence vs. mixed vs. other) using polynomious regression.

Using multivariable logistic regression analysis, we will also generate predictive probabilities for various combinations of history, bladder wall thickness and urodynamics results. We have experience of undertaking such analysis to estimate predictive probabilities. (24) Historical features to be included in the regression model will include age, menopausal status, parity, body mass index, presence of mixed symptoms and previous antimuscarinic treatment. In statistical terms, logistic modelling will aim to derive a diagnostic regression function, i.e. probability of DO given test result. The analysis will be performed with UDS reference diagnosis of DO as the outcome variable and BUS as an explanatory variable. The models will allow a direct estimation of the post-test-combination disease probabilities that we need for decision-making and for decision-analysis. Models of varying complexity may be compared through the familiar receiver operating characteristic (ROC) analyses. More importantly, the clinical situation where some information is already acquired, such as clinical symptoms prior to undertaking BUS, will be mirrored. In this way, for various index test results conditional disease probabilities will be generated directly taking into account any overlap of information that may exist between tests. This approach evaluates the extent to which the findings of the index tests add value to the presentation. Its output is transparent, and is likely to enable production of simple clinical algorithms based on probabilities. The advantages of tackling diagnostic problems with logistic regression modelling are well known.(25) The limitation associated
with the regression approach lies mainly in its generalisability to other data sets or clinical practices. The recommended techniques, such as bootstrapping to enhance generalisability and estimate the amount of shrinkage will be applied for model validation.(26,27) We anticipate that our sample will comfortably meet the recommended events per variable rule to avoid overfitting the models even if some data were missing. In a sensitivity analysis, missing data will be estimated by multiple imputation and maximum-likelihood methods, as appropriate, to explore the potential bias and reduced statistical power associated with list wise deletion.

**Subgroup analyses**

Our literature review (8) and consultations suggests that the accuracy of the index tests may vary according to other variables (previous treatment with antimuscarinics, clinical history suggesting mixed incontinence i.e. concomitant urodynamic stress incontinence, presence of urinary tract infections in the past 12 months, voiding difficulties, patients who also have ambulatory urodynamics for DO verification, past history of continence surgery etc.). For this study, we intend to consider laboratory multichannel urodynamics as the reference standard but we will also look at the subgroup of patients who have ambulatory UDS in addition (based on clinician’s judgement and availability) separately, because there is some evidence that this test is more sensitive at picking DO. (21) We will also look at the diagnostic accuracy of BUS in women with mixed incontinence in subgroup analysis as there is some suggestion that this might be different in presence of a isolated or concomitant incompetent sphincter.(12) Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. Therefore, we have chosen to limit secondary analyses to these subgroups only. All estimates of accuracy for subgroups will be interpreted with appropriate caution.

6.4. Handling missing data

Sensitivity analysis will be employed to explore the potential bias and reduced statistical power associated with listwise deletion of missing data, using multiple imputation and maximum-likelihood methods, as appropriate.(28)

6.5. Economic analysis

6.5.1 Model and analysis

The economic evaluation will involve the development of a decision analytic simulation model as a framework for conducting cost-effectiveness analysis. The modelling framework will allow additional exploration of scenarios that are not being specifically explored as part of the primary study such as using the ultrasound test at different time points through the duration of the study (based on an assumption that the accuracy would remain unchanged). We can also explore, from an economic perspective, what is likely to be the most cost-effective threshold (cut off value) for the BUS diagnostic test. A modelling framework is ideally suited to demonstrate and explore these issues and also the importance of the inherent uncertainty.

The decision analysis model will be constructed using TreeAge Pro software. This is a widely-used and highly user-friendly package ideally suited to the construction and analysis of decision trees and other models.
6.5.2 Discounting
An incremental approach will be adopted with a focus on additional costs and gain in benefits associated with a move away from current practice to alternative test and treatment strategies. Using discounting, adjustments will be made to reflect this differential timing. The base-case analysis will follow Treasury recommendations for public sector projects.

6.5.3 Presentation of results and sensitivity analysis
The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. Both simple and probabilistic sensitivity analyses will be used to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.

7. DATA ACCESS AND QUALITY ASSURANCE

7.1. In-house Data Quality Assurance

7.1.1 Monitoring and Audit
Staff performing the BUS test will be trained by the co-applicant radiologist, the PI or clinical research fellow, who will review their skills regularly. A sample of test results inputted in the participating units will be cross-checked at the BUS Study Office with paper or electronic records.

7.1.2 Statistical monitoring throughout the study
Real-time reports will be available to staff indicating missing test and questionnaire data for all participants at that centre. This will be supplemented by regular reminders from the BUS Study Office for incomplete data. The study statistician will report on recruitment, compliance and completeness of verification to the Steering Committee quarterly.

7.2. Independent Supervision of the Study
The Study Steering Committee provides independent supervision for the study, providing advice to the investigators and the Sponsor on all aspects of the study and affording protection for patients by ensuring the study is conducted as applicable to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the clinical co-ordinators are unable to resolve any concern satisfactorily, collaborators, and all others associated with the study, may write through the study office to the chair of the SSC, drawing attention to any concerns they may have about the possibility of distortion of clinical practice, or of particular categories of patient requiring special study, or about any other matters thought relevant.

The study shall follow and comply with the MRC Guidelines on Good Clinical Practice, although its advice in relation to test accuracy studies is limited. The Study Team has made provisional recommendations regarding the independent supervision and data monitoring of test accuracy studies as a consequence of experiences in previous studies. (29) One such recommendation is that, if desirable, the independent Data Monitoring and Ethics Committee (DMEC) should be formed as a sub-committee of the Study Steering Committee (SSC). For the purposes of this study, the SSC shall convene and nominate a
three member independent DMEC from within its membership, that shall not include study researchers.

7.3. Data Monitoring and Ethics Committee: determining when clear answers have emerged

The BUS test may be found to be unworkable, new evidence of the effectiveness of the test might emerge from other sources or new technologies may be introduced to the market.

To protect against this, at 6 months into recruitment to the study, interim analyses of major endpoints will be supplied to the DMEC along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will determine whether the assumptions underpinning the sample size are correct at 6 months after commencement of recruitment. The interim analysis will also determine if the principal question on index test accuracy has been answered and will monitor adverse events. The combined SSC/ DMEC (a) should consider the balance of harms and risks in the context of all available data, and make recommendations on the principle of “proof beyond reasonable doubt” and (b) consider evidence that might reasonably be expected to influence the patient management of many clinicians. The SSC/DMEC can then decide whether to close or modify any part of the study. Unless this happens, however, the SSC, the collaborators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

8. ORGANISATION AND RESPONSIBILITIES

The Chief Investigator is responsible for the management, central co-ordination of clinical and administrative aspects of the study, compliance with the Research Governance Framework and management of study budget. Relevant ethics committee and Trust research governance approval will be coordinated centrally for efficiency and speed.

All investigators are responsible for ensuring that the research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse reactions and other events or suspected misconduct through the appropriate systems.

8.1. Centre eligibility and funding

Centres that have facility for UDS and TVS will be able to recruit women into the study. The urogynaecology research nurse or research fellow based at Birmingham Women’s Hospital, employed for this project, will support the sites within the city of Birmingham. Per patient payments will be available for the first 300 patients recruited and this could be used to fund a regular research nurse session or sonography session to help with the study in the non Birmingham participating centres. This payment will only be available for patients who complete all their baseline assessments, and the two tests, within the prescribed time period of 4 weeks.

8.2. Local Co-ordinator at each centre

Each Trust has a designated Consultant urogynaecologist or urologist or nurse specialist to act as Principal Investigator and bear responsibility for the conduct of research at their centre. The responsibilities of the Principal Investigators will be to ensure that all medical
and radiography staff involved are well informed about the study. This will involve distributing protocols and patient information sheets to all relevant staff, displaying publicity material where it is likely to be read, and contributing to the regular newsletters. The Principal Investigators should liaise with the BUS Study Office on logistic, data collection and administrative matters connected with the study.

8.3. Nurse Co-ordinator at each centre
Each participating centre should have a designated research nurse who will act as Local Nurse Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse will be responsible for the organisation of data collection and will be the first point of contact for data queries.

8.4. The Study Office
The Study Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all study materials, including the coded stickers and questionnaires. Additional supplies of any printed material can be obtained on request. The Study Office is also responsible for collection and checking of data (including reports of serious adverse events) and for analyses. The Study Office will help resolve any local problems that may be encountered in study participation and will supply accrual data to the NIHR on behalf of each centre.

8.5. Research Governance
The conduct of the study will be according to the principles of MRC Guidelines for Good Clinical Practice in Clinical Trials (1998) and the appropriate NHS Research Governance Frameworks.

All centres will be required to sign an Investigator’s Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the SSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre. Proof of training in the principles of good clinical practice and informed consent may be required.

The Study Office will ensure researchers not employed by an NHS organisation who interact with individuals in a way that has direct bearing on the quality of their care hold an NHS honorary contract for that organisation.

8.6. Regulatory and Ethical Approval
The Chief Investigator has obtained a favourable ethical opinion from Nottingham Multi-centre Research Ethics Committee (MREC). Each Trust Research and Development Office will assess each site for “locality issues” relating to their population, the investigators, the facilities and resources and grant site specific approval before recruitment commences.

8.7. Funding and Cost implications
The research costs of the study are funded by a grant from the National Institute for Health Research (NIHR) Health Technology Assessment Unit awarded to the University of Birmingham.
The study has been designed to minimise extra ‘service support’ costs for participating hospitals, with no extra visits to hospital and no extra tests. Additional costs associated with the study should be minimal. These costs should be met by accessing the Trust’s budget.

The BUS trial will automatically be included in the NIHR portfolio, which allows local investigators and their Trust to access additional support for the study, for example regular nurses sessions to support clinics. This may be provided directly from the Trust’s service support allocation or via the local comprehensive research network. The BUS Study Coordinator will assist local investigators in accessing this support.

8.8. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored study and so ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96(48) will operate in this case. However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical study. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

8.9. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Collaborators will be permitted to publish data obtained from participants in the BUS Study that use study outcome measures but do not relate to the study objectives. All the results from the study will be published under BUS collaboration team’s name and the collaborators, with names of centres, will be listed at the end of the manuscript. This does mean that all the collaborators will be PUBMED indexed.
References


(23) Cheng H., Macalouso M. Comparison of the accuracy of two tests with a confirmatory procedure limited to positive results. Epidemiology 1997;8:04-106.


APPENDIX A: PATIENT CONSENT FORM:

Accuracy of Bladder Ultrasound Study (BUS)

I confirm that I have read and understand the information sheet (version 2.0, dated 25/7/2012) for the above study and have had the opportunity to consider the information, to ask questions and these have been answered satisfactorily.

I understand what is involved in the BUS study and agree to participate. I intend to participate in the study, but I understand that I am free to change my mind when I go into hospital without necessarily giving a reason. If I do withdraw, I can continue to expect the highest standard of care from my doctor or nurse.

I understand that my doctors will provide a copy of my consent form and personal information about my progress, in confidence, to the central organisers at Birmingham Clinical Trials Unit (BCTU) for use in the BUS Study.

I understand that the information will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of Birmingham or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

*I consent to my GP being informed that I am participating in the BUS study and being contacted if we need to trace you.

I consent to being contacted by a member of the BUS study research team for the purpose of obtaining any missing baseline data and for follow-up of my condition after my test appointment(s), and I am happy to provide contact details for myself and my GP for this purpose only.

Name of Participant                                      Date                                      Signature

**AT TIME OF UDS TESTING**

I still agree to participate in the BUS Study

Name of Participant                                      Date                                      Signature

Name of Person taking consent                           Date                                      Signature

Name of Interpreter                                      Date                                      Signature

*Consent can go ahead without the need for GPs to be informed.
4 copies: Original copy for BUS site file, 1 copy for patient, 1 copy to be kept in patient’s hospital notes and 1 copy to be sent to BUS Study Office.
APPENDIX B: REGISTRATION FORM

Accuracy of Bladder Ultrasound Study (BUS)

REGISTRATION FORM

To be completed before registering participant into the BUS Study

PART A: IDENTIFICATION DETAILS

Consultant: _______________________________ Hospital: _______________________________

Patient’s surname: ___________________________ Patient’s Forenames: ___________________________

Patient’s title: Mrs Miss Ms Dr Other: ______________________ Date of birth: __________ __________

Patient NHS No.: ___________________________ Patient hospital no.: ___________________________

Patient’s address: ____________________________________________ Postcode: _______________________

Patient’s daytime telephone number: ___________________________ Evening telephone number: ___________________________

Mobile telephone number: ___________________________ Patient’s email: ___________________________

Ethnic Group:

White

British

Irish

Other White

Black / Black British

Caribbean

African

Other Black

Asian / Asian British

Indian

Pakistani

Bangladeshi

Other Asian

Mixed

Mixed White/ Black Caribbean

Mixed White/ Black African

Mixed White/ Asian

Other Mixed Background

PART B: ELIGIBILITY

Yes No

Baseline Frequency and Volume chart checked? ☐ ☐

>8 voids in 24 hours on any one of 3 days? (taken from Frequency/Volume Chart) ☐ ☐

At least two episodes of urgency in 3 days (mild-severe)? (taken from Frequency/Volume Chart) ☐ ☐

Symptoms of cystitis (dysuria + frequency)? ☐ ☐

Leucocytes OR Nitrite positive? ☐ ☐

Postvoid residual >100 mls? ☐ ☐

Had urodynamics in last 6 months? ☐ ☐

Recent use of antimuscarinics? ☐ ☐

If Yes, has medication been taken in the last 2 weeks prior to USS or UDS? ☐ ☐

Use of antimuscarinics for more than 6 months continuously? ☐ ☐

Has the patient given written informed consent? ☐ ☐

If both stress and urge incontinence present, is urgency/urge incontinence the predominant symptom? ☐ ☐

Previous stress incontinence surgery &/or Botox? ☐ ☐

If Yes, has surgery/botox been undertaken within the last 6 months? ☐ ☐

Prolapse > grade II (any compartment) ☐ ☐

Pregnancy and up to 6 weeks postpartum? ☐ ☐

PART C: STUDY REGISTRATION (COMPLETE AT THE TIME OF PHONE CALL ONLY)

TO REGISTER CALL 0800 9530274

BUS study number: ☐ ☐ ☐ ☐

If any of the shaded boxes are ticked, the patient is NOT eligible for the BUS Study.
BUS Contact name: ................................................ Telephone:..............................................................
APPENDIX C: LETTER TO GP

Accuracy of Bladder Ultrasound Study (BUS)

Doctor
Practice
Street
City
Postcode

Date

Dear Dr <gp name>

Name............................................................D.o.B....................NHS No...........................

Your patient, named above, has been referred to <centre> for assessment of urinary symptoms, and is suitable for entry to the BUS Study: **Accuracy of Bladder Ultrasound in the diagnosis of overactive bladder: a study to evaluate if ultrasound can reduce the need for urodynamics**

The University of Birmingham is acting as sponsor. The University of Birmingham Clinical Trials Unit are acting as coordinating centre. The study is funded NIHR Health Technology Assessment Programme. The study has been approved by the Nottingham Research Ethics Committee 2 and approvals have been obtained at each participating centre.

Your patient has been informed about the BUS study, has consented to take part and will undergo both transvaginal ultrasound to measure bladder wall thickness and urodynamics test. We will inform you of the diagnosis and recommended management in due course.

If you have any queries about the patient's management, please feel free to contact me. If you require any further information about the BUS study, it can be obtained from the BUS trial office (see address below). Please file this letter in the patient’s notes. I would appreciate being notified if they are no longer one of your patients.

Yours sincerely

Name
Position

BUS Study Office, FREEPOST RRKR-JUZR-HZHG, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT
Tel: 0121 415 9108; Fax: 0121 415 9136; Email: bus-study@contact.bham.ac.uk ; Website: www.BUS.bham.ac.uk
APPENDIX D SERIOUS ADVERSE EVENT FORM

SERIOUS ADVERSE EVENT FORM

Please report any serious, unexpected adverse events* believed to be due to the treatments given as part of the BUS study by sending or faxing the following details to the Study Office (fax: 0121-415-9136) within 2 weeks of the event:

Patient’s Full Name: 
Date of Birth: ___________________________ Hospital Number: ___________________________
Responsible doctor: ______________________________________________________________
Hospital name: ________________________________________________________________
Date and type of test: _____________________________________________________________
Date Event Started: ___________________________ Date Event Ceased: ___________________________
Outcome (e.g. fatal, recovered, continuing): _______________________________________________

Details of Adverse Event (please attach copies of relevant reports)

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________

Did the event require or prolong hospitalisation? ___________________________

Please give reasons why you consider the event to be test-related:

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________

Name of Person Reporting (please print)

Telephone Number: ___________________________ Today’s Date: ___________________________

* For the purposes of this study, “serious” adverse events are those which are fatal, life-threatening, disabling or require hospitalisation. “Unexpected” adverse experiences are defined as those that would not be expected as a result of ultrasound or urodynamic testing. It is not required to report in this way side-effects or events that might reasonably be expected.
Accuracy of Bladder Ultrasound Study (BUS)

PATIENT INFORMATION SHEET and CONSENT FORM COVER SHEET

For more information about the study at <CENTRE>, <TRUST> contact:

Your nurse/doctor: <Recruiting clinician>
Phone number:

Or lead doctor: <Local PI, if not recruiting clinician>
Phone number:

For more information about your hospital or to make a complaint:

PALS, <CENTRE>, <TRUST address and phone number>

For more information from the BUS study organisers:

<Clinical Research Fellow>
Phone number:
www.bus.bham.ac.uk
APPENDIX F PATIENT INFORMATION SHEET:

ACCURACY OF BLADDER ULTRASOUND STUDY (BUS)

BUS Participant Information Sheet – this tells you the purpose of the study and what will happen to you if you take part

Invitation to participate in the BUS study

We would like to invite you to take part in a research study that may help to reduce the need for invasive tests called urodynamics. The decision to take part will be yours, you do not have to join in or give us the reason why you choose not to. It is important for you to understand why the research is being done and what it will involve. Discover more by reading the following information. Feel free to spend time discussing it with anyone - it may help to talk to a member of the research team.

What is the purpose of the study?

☐ Overactive bladder syndrome is often described as urgency that occurs with or without incontinence and usually with an increased frequency of urination and the need to go to toilet in the night.

☐ In a UK study, overactive bladder symptoms were found in 12% of the general population. In individuals over 40 years of age, 34% report significant lower urinary tract symptoms.

☐ Urinary symptoms alone cannot be used to diagnose overactive bladder syndrome, so some doctors recommend a test called urodynamics. With this test, we can diagnose whether the bladder muscles are overactive (detrusor overactivity).

☐ Urodynamics involves a catheter inserted in the urethra (the tube from the bladder to outside of the body) which can cause discomfort and carries a small risk of infection.

☐ An alternative is to measure the thickness of the bladder wall by ultrasound. This is a simpler, more, comfortable test.

☐ We do not know for certain how accurate ultrasound will be at detecting detrusor overactivity that is why we are undertaking this research study.

Who is organising and funding the research?

The BUS study is funded by a grant from the NHSR Health Technology Assessment programme. The central study organisers are based at the University of Birmingham. This study has been reviewed and given favourable opinion by Nottingham Research Ethics Committee 2. The Clinical Trials Unit at the University of Birmingham will collect and analyse the data. The researchers, doctors and nurses involved are not being paid for recruiting women into the study. We cannot pay women to take part either, but we will be very grateful for their help in finding out more about the accuracy of this test.

Do you have any other questions?

Having read this leaflet, we hope that you will choose to take part in the BUS Study. If you have any questions about the study now or later, feel free to ask the personnel whose names and telephone numbers are given on the below.

What if I have any concerns?

If you have any concern or other questions about this study or the way it has been carried out, you should contact the chief investigator Dr. Pallavi Lathra, or you may contact your hospitals Patient Advisory and Liaison Service or local equivalent.

What else do I have to do?

We (the researchers) would also like a sample of women to answer some questions about acceptance. You may be given an anonymous questionnaire to complete before you leave hospital as we want to find out the how you found the tests and the research study.

What are the possible disadvantages and risks of taking part?

We hope that the test results will help you get the most appropriate treatment for your urinary symptoms without further tests. However, there may be no benefits from taking part.

Also, of course, the information we get from this study may in the future help us reduce the need for urodynamics in women with overactive bladder.

(For more information from the BUS study organisers (to be entered here)

What if something goes wrong?

We do not believe that there is a risk of anything going wrong. However, if you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?

Yes, all information collected in the study will remain strictly confidential in the same way as your other medical records. If you agree to take part, your nurse or doctor will send basic information about you to the study’s central organisers. This information will be put into a computer and analysed. The questionnaires will be identified only by a code number and will not be seen by your doctor or nurse.

All information will be held securely and in strict confidence. No named information about you will be published in the study report. Occasion-ally, inspections of clinical study data are undertaken to ensure that, for example, all participants have given consent to take part. But, apart from this, only the study organisers will have access to the data.

With your consent we will inform your GP of your participation in the BUS Study.

What will happen to the results of the research study?

The study will last for around three years, after which we expect to publish the results in scientific journals. We will send you a summary of the results by post.

The BUS Study is organised by the University of Birmingham Clinical Trials Unit.

For further information please visit our website:
http://www.bctu.bham.ac.uk/bus

or email us on:
bus-study@contact.bham.ac.uk
Commonly asked questions?

Why have I been chosen?
All women who have been referred to this hospital by the GP with symptoms of increasingly frequent toilet visits or feel a sudden urgent need to pass urine are being invited to take part. It is hoped 600 women from several hospitals will take part in the study.

When do I have to decide?
It is up to you to decide whether or not to join the study. You will be asked to bring this information sheet and consent form with you when you come to the clinic as you will be asked at your hospital clinic appointment whether you are willing to take part. If you agree, you will be asked to sign the consent form (identical to the sample overhead).

At the time of testing, you will be asked again if you still agree to participate. You are free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to participate, will not affect the standard of care you receive.

What will happen to me if I take part?
If you agree to take part, we will measure the bladder wall thickness by means of an ultrasound examination, which obtains images of the body without the use of X-rays. In order to perform this scan it is necessary to gently insert the tip of an ultrasound probe into the vagina. This is a simple and usually painless procedure. The probe is a little bigger than the size of a finger or a tampon, and produces pictures on a TV screen. The test will take no more than five minutes to perform.

You will then have the test called urodynamics. An information sheet for this test is attached with this leaflet. This is the test which the doctors may perform regardless of whether you are in the study.

For more information about your hospital or to make a complaint please contact:

(Individual Trust PALS details to be entered here)