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Extended Research Article

Invasive urodynamic investigations in the management of women with refractory overactive bladder symptoms: FUTURE, a superiority RCT and economic evaluation

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Disclaimer

This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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This article

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Abstract

Background: Overactive bladder is a common problem affecting the United Kingdom adult female population. Symptoms include urinary urgency, with or without urgency incontinence, increased daytime urinary frequency and nocturia.

Initial conservative treatments for overactive bladder are unsuccessful in 25–40% of women (refractory overactive bladder). Before considering invasive treatments, such as botulinum toxin injection-A or sacral neuromodulation, guidelines recommend urodynamics to confirm diagnosis of detrusor overactivity. However, the clinical and cost effectiveness of urodynamics has never been robustly assessed.

Objectives: To compare the clinical and cost effectiveness of urodynamics plus comprehensive clinical assessment versus comprehensive clinical assessment only in the management of refractory overactive bladder in women.

Design: Parallel-group, multicentre, superiority, open-label, randomised controlled trial. Allocation by remote web-based randomisation (1 : 1 ratio). The cost-effectiveness analysis took the National Health Service perspective with a model-based lifetime time horizon, as informed by a within-trial analysis.

Setting: Sixty-three United Kingdom secondary and tertiary hospitals.

Participants: Women aged ≥ 18 years with refractory overactive bladder or urgency-predominant mixed urinary incontinence who had failed conservative management and pharmacological treatment and were being considered for invasive treatment. Women were excluded if any of the following criteria were met: predominant stress urinary incontinence; previous urodynamics in last 12 months; current pelvic malignancy or clinically significant pelvic mass; bladder pain syndrome; neurogenic bladder; urogenital fistulae; previous treatment with botulinum toxin injection-A or sacral neuromodulation for urinary incontinence; previous pelvic radiotherapy; prolapse beyond introitus; pregnant or planning pregnancy; recurrent urinary tract infection where a significant pathology has not been excluded; and inability to give an informed consent.

Interventions: Urodynamics plus comprehensive clinical assessment (urodynamics arm) versus comprehensive clinical assessment only.

Main outcome measures: Participant-reported success at the last follow-up time point as measured by the Patient Global Impression of Improvement. Primary economic outcome was incremental cost per quality-adjusted life-year gained as modelled over the lifetime of participants.

Results: A total of 1099 participants were included: 550 randomised to the urodynamics arm and 549 to the comprehensive clinical assessment only arm. At the final follow-up time point, participant-reported success rates of 'very much improved' and 'much improved' were not superior in the urodynamics arm (117 participants; 23.6%) compared to the comprehensive clinical assessment only arm (114 participants; 22.7%) [adjusted odds ratio 1.12 (95% confidence interval 0.73 to 1.74); $p = 0.601$]. Serious adverse events were low and similar between groups.

Based on the estimated incremental costs and quality-adjusted life-years of urodynamics (£463 and 0.011, respectively), the incremental cost-effectiveness ratio was £42,643 per quality-adjusted life-year gained. The cost-effectiveness acceptability curve shows that urodynamics has a 34% probability of being cost-effective at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year gained. This probability reduced further when the results were extrapolated over the patient's lifetime. Limitations include: only short-term outcomes were available, and as most participants underwent botulinum toxin injection-A treatment, pre-planned secondary analyses for some outcomes such as sacral neuromodulation were not possible.

Conclusion: Participant-reported success in the urodynamics arm was not superior to the comprehensive clinical assessment only arm at 15-months follow-up. Urodynamics is not cost-effective at a threshold of £20,000 per quality-adjusted life-year gained. Longer-term follow-up is required to explore need for further interventions and treatments and their effect on the clinical and cost-effectiveness analyses.

Trial registration: This trial is registered as ISRCTN63268739.

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Report Supplementary Material 1 Statistical and health economics analysis plans

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/UKYW4923).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
BMI	body mass index
BNF	*British National Formulary*
BoNT-A	botulinum toxin injection A
BUS	Bladder Ultrasound Study
CCA	comprehensive clinical assessment
CEAC	cost-effectiveness acceptability curve
CEP	cost-effectiveness plane
CHaRT	Centre for Healthcare Randomised Trials
CISC	clean intermittent self-catheterisation
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease-19
CRF	case report form
DMC	Data Monitoring Committee
DO	detrusor overactivity
DOI	detrusor overactivity incontinence
EPINCONT	Epidemiology of Incontinence in the County of Nord-Trøndelag
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FUTURE	Female Urgency, Trial of Urodynamics as Routine Evaluations
GLM	generalised linear model
GP	general practitioner
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICIQ	International Consultation on Incontinence Questionnaire
ICIQ-FLUTS	ICIQ female lower urinary tract symptoms
ICIQ-LUTS	ICIQ lower urinary tract symptoms
ICIQ-LUTSQoL	ICIQ lower urinary tract symptoms quality of life
ICIQ-OAB	ICIQ overactive bladder
ICIQ-SF	ICIQ short form
ICIQ-UI-SF	ICIQ urinary incontinence short form
ICS	International Continence Society
ITT	intention to treat
KHQ	King's Health Questionnaire
LUTS	lower urinary tract symptoms
MDT	multidisciplinary team
MRC	Medical Research Council
MUI	mixed urinary incontinence
NHSG	NHS Grampian
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OAB	overactive bladder
PFM	pelvic floor muscle
PFMT	pelvic floor muscle training
PGI-I	Patient Global Impression of Improvement
PI	principal investigator
PIL	patient information leaflet
PMG	Project Management Group
PPI	patient and public involvement
PSA	probabilistic sensitivity analysis
PTNS	percutaneous tibial nerve stimulation
PVR	post-void residual
QA	quality assurance
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SF	short form
SNM	sacral neuromodulation
SNS	sacral nerve stimulation
SUI	stress urinary incontinence

TSC	Trial Steering Committee	USI	urodynamic stress incontinence
UI	urinary incontinence	UTI	urinary tract infection
UPS	Urgency Perception Scale	UUI	urgency urinary incontinence

Plain language summary

Overactive bladder affects 12–14% of United Kingdom women. Initial treatments include lifestyle changes, pelvic floor exercises, bladder training and tablets. Sometimes these treatments do not work, with many women requiring more invasive procedures.

Before having these procedures, it is normal United Kingdom practice to have an invasive test called urodynamics.

Some women find urodynamics embarrassing and/or uncomfortable. After the test, some get cystitis (a urine infection) and in about one-third of women urodynamics does not show the cause of their overactive bladder symptoms. This may result in some women not being offered treatments which may help their condition.

In this study, 1099 women who were looking for invasive treatments agreed to take part. They were randomly allocated to receive urodynamics plus a clinical assessment (550 women) or a clinical assessment only (549 women). The clinical assessment included a detailed medical history, clinical examination, bladder diary and non-invasive tests. We compared the two groups by asking the women about their symptoms throughout the study.

Slightly fewer women in the urodynamics group received treatment during the study. Of those who did receive treatment, an injection of Botox into the bladder wall was the most common treatment in both groups. There was no difference in complications between the groups.

At the end of the study, women in both groups reported an improvement in their quality of life. The number of women who said their symptoms were 'very much improved' or 'much improved' was similar between the groups [117 women (23.6%) in the urodynamics group compared with 114 women (22.7%) in the clinical assessment only group]. The additional cost to the National Health Service in receiving urodynamics was £463.

The views of the women interviewed during the study varied, with some saying they were willing to have urodynamics if it helped with treatment decisions, while others were extremely worried about the discomfort and embarrassment of the procedure.

This study suggests that performing urodynamics before invasive treatment does not lead to an improvement in women's overactive bladder symptoms compared to comprehensive clinical assessment only (i.e. is not superior) and is more expensive. However, further work is under way to confirm this in the longer term.

Scientific summary

Background

Overactive bladder (OAB) affects 12–14% of the UK adult female population. Symptoms include urinary urgency, with or without urgency incontinence, increased daytime urinary frequency and nocturia. OAB has a negative impact on women's social, physical and psychological well-being. Initial treatment includes lifestyle modifications, bladder retraining, pelvic floor exercises and pharmacological therapy. However, these measures are unsuccessful in 25–40% of women (refractory OAB). Before considering invasive treatments, such as botulinum toxin injection A (BoNT-A) or sacral neuromodulation (SNM), most guidelines recommend urodynamics to confirm diagnosis of detrusor overactivity (DO). However, urodynamics may fail to show evidence of DO in up to 45% of cases, hence the timely need to evaluate its clinical and cost effectiveness.

Objectives

To compare the clinical and cost-effectiveness of urodynamics plus comprehensive clinical assessment (CCA) versus CCA only in the management of refractory OAB symptoms in women.

Design

Female Urgency, Trial of Urodynamics as Routine Evaluations (FUTURE) was a parallel-group, multicentre, superiority, randomised controlled trial. The cost-effectiveness analysis took the NHS perspective with a model-based lifetime time horizon, as informed by a within-trial analysis.

Setting

FUTURE involved 63 secondary and tertiary hospitals across the UK.

Participants

Women aged 18 years and over with refractory OAB or urgency-predominant mixed urinary incontinence (MUI), who had failed conservative management and pharmacological treatment and were being considered for invasive treatment, were invited to participate.

Women were excluded if any of the following criteria were met: predominant stress urinary incontinence (SUI); previous urodynamics in last 12 months; current pelvic malignancy or clinically significant pelvic mass; bladder pain syndrome; neurogenic bladder; urogenital fistulae; previous treatment with BoNT-A or SNM for urinary incontinence; previous pelvic radiotherapy; prolapse beyond introitus; pregnant or planning pregnancy; recurrent urinary tract infection where a significant pathology had not been excluded; and inability to give an informed consent.

Interventions

Eligible and consenting participants were randomised to one of the following two treatment arms in a 1 : 1 allocation ratio using a remote web-based randomisation service:

- urodynamics plus CCA (urodynamics arm)
- CCA only (CCA only arm).

The randomisation process used stratified random permuted blocks with (1) site and (2) diagnosis of OAB versus urgency-predominant MUI used as strata.

Main outcome measures

The primary clinical outcome measure was participant-reported success at their last follow-up time point (either 15 or 24 months post randomisation) as measured by the Patient Global Impression of Improvement (PGI-I). Success was defined as participant response of 'very much improved' or 'much improved'. The primary economic outcome was incremental cost per quality-adjusted life-year (QALY) gained.

Secondary outcome measures included: a less strict definition of success at the last follow-up time point where success was defined as 'very much improved', 'much improved' or 'improved'; proportion of women receiving invasive treatment during follow-up; participant-reported success in the first 2 months following BoNT-A (for women who received BoNT-A only); OAB symptoms measured by the International Consultation on Incontinence Questionnaire (ICIQ) overactive bladder (ICIQ-OAB) and the Urgency Perception Scale (UPS); urgency and urgency urinary incontinence episodes measured using the 3-day bladder diary; other urinary symptoms measured using the three domains of ICIQ female lower urinary tract symptoms (ICIQ-FLUTS; filling, voiding and incontinence) and the bladder diary; general health-related quality of life (HRQoL) status measured using generic [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)] and condition-specific [ICIQ-LUTSQoL (ICIQ lower urinary tract symptoms quality of life)] assessment tools; adverse events; cost; and cost-effectiveness.

Data collection during follow-up

Participant-reported outcomes were assessed by self-completed questionnaire at baseline and 3, 6 and 15 months post randomisation. An additional 24-month post-randomisation questionnaire was completed by participants whose treatment had been delayed by the COVID-19 pandemic. A self-completed 3-day bladder diary was also collected at baseline and 6 and 15 months post-randomisation.

Sample size

Outcome data were required on 986 participants per group for 90% power to detect a minimum of 10% superiority of urodynamics over CCA only. Based on an expected 10% drop-out rate, the recruitment target was 1096 participants in total (548 participants per group).

Statistical analysis

Analyses were conducted in adherence with the intention-to-treat principle. Analyses used a two-sided 5% significance level with corresponding 95% confidence intervals (CIs). The primary outcome was analysed using repeated-measures mixed-effects logistic regression. Secondary outcomes were analysed using the appropriate generalised linear model.

Economic evaluation

The economic analysis consisted of a within-trial analysis up to 24 months and a decision-analytic modelling framework to inform cost-effectiveness over a lifetime horizon. Costs and outcomes were collected on participant questionnaires and case report forms. EQ-5D-5L scores were used to estimate QALYs. Costs took the NHS perspective and were calculated at 2020–1 price levels. Increments were estimated using regression models with multiple imputation. Deterministic sensitivity analyses examined a complete-case analysis, a societal perspective and alternative utility and cost estimates. Probabilistic sensitivity analyses were undertaken. A subgroup analysis based on initial diagnosis was undertaken. To estimate longer-term economic differences, a hybrid model with a decision tree describing short-term events and Markov processes describing long-term events was developed using external evidence that captures clinical and patient events beyond the end of the trial.

Qualitative interviews

The principal aim of the qualitative interviews was to establish the perspectives of clinicians and patients in the decision-making processes regarding investigation for refractory OAB, and participant perspectives following treatment.

The qualitative data management software NVivo 10 (QSR International, Warrington, UK) was used to conduct the analyses. Purposive sampling was used to identify potential participants already recruited into FUTURE. Recruitment continued until data saturation was reached and there were no new emerging themes. Telephone interviews were audio-recorded and transcribed verbatim, and data transcripts were coded and analysed using a thematic analysis.

Management of the study

The study was supervised by the project management group, which consisted of representatives from the study office and grant holders. The study was further overseen by an independent Trial Steering Committee, and an independent Data Monitoring Committee.

Results

Recruitment

Between November 2017 and January 2021, 3066 potentially eligible participants were screened, 1511 (49.3%) confirmed eligible and 1103 (73.0%) gave their consent and were randomised. There was a pause in recruitment between March 2020 and August 2020 due to the COVID-19 pandemic. Following randomisation, four participants were considered ineligible and recorded as post-randomisation exclusions. Therefore, 1099 participants (550 in the urodynamics arm and 549 in the CCA only arm) were included in the trial.

Baseline characteristics

At baseline, both groups were similar, with a mean age of 60 and a mean body mass index of 31. Two-thirds of the population were clinically classified as OAB, with the remaining third as urgency-predominant MUI. Urgency was classed as severe by 64% and 63% of the respective groups. All participants had received previous conservative treatment, with bladder training and pelvic floor muscle training being the most common conservative treatment received (69% and 84% respectively).

At baseline the EQ-5D-5L scores were 0.653 and 0.674 respectively, a lower quality-of-life score than the population mean for this age group.

Clinical effectiveness

At the final follow-up time point, there was no significant difference between the success rates on the PGI-I: urodynamics arm 23.6% (117/496) versus CCA only arm 22.7% (114/503), odds ratio (OR) 1.12 (95% CI 0.73 to 1.74); $p = 0.60$. This is consistent with the effect sizes obtained for the less strict definition of success and when multiple imputation was used as a sensitivity analysis. The per protocol analysis was also consistent and showed no significant difference between the groups: urodynamics [113/454 (24.9%)] vs. CCA only [111/483 (23.0%)], OR 1.22 (95% CI 0.78 to 1.91); $p = 0.39$. The subgroup analysis comparing OAB to urgency-predominant MUI also did not show any significant difference in the effect of urodynamics [1.14 (99% CI 0.33 to 3.90); $p = 0.79$] nor did restricting the PGI-I assessment to those who received BoNT-A and rated their success '2 months following treatment' (63.8% vs. 60.0% [OR 1.17 (99% CI 0.73 to 1.89); $p = 0.52$]). Women in the CCA only arm were significantly more likely to show earlier improvement in their symptoms, that is, at 3-month follow-up [OR 0.35 (95% CI 0.19 to 0.66); $p = 0.001$].

Secondary outcomes

On the UPS, there was improvement in urgency perception between baseline and final follow-up in both groups, with the effect sizes for level of urgency [OR 0.87 (95% CI 0.63 to 1.21); $p = 0.42$], cure [OR 2.04 (95% CI 0.86 to 4.80); $p = 0.10$] and improvement [OR 1.12 (95% CI 0.78 to 1.62); $p = 0.53$] showing no significant difference between groups.

In both groups there was improvement on the ICIQ-OAB score from baseline to the final follow-up. At final follow-up, the difference tended to favour urodynamics but was not significant [adjusted mean difference −0.4 (95% CI −0.9 to 0.0); $p = 0.06$].

On both the ICIQ-FLUTS filling and incontinence domain scores there was improvement from baseline to final follow-up in both groups, with no significant differences between groups, except for the filling domain score favouring

urodynamics [adjusted mean difference −0.4 (95% CI −0.9 to −0.0) p = 0.04]. No improvement from baseline was observed on the voiding domain nor was there a significant difference between the groups.

There was no difference between the groups in HRQoL on the specific ICIQ-LUTSQoL score nor the more generic EQ-5D-5L, although there was an indication of improvement from baseline on the former. Interference in everyday life from urinary symptoms was similar between the groups at all time points.

Treatments received

The percentage of CCA only participants receiving any treatment following assessment was slightly higher than for the urodynamics group [87.2% (479/549) vs. 84.9% (467/550)]. The treatments with the highest frequencies were BoNT-A, medical treatment and physiotherapy. Of those receiving treatment, the percentage of participants receiving BoNT-A was higher in the CCA only group [71.6% (343/479)] compared to the urodynamics group [59.3% (277/467)]. The other invasive treatments of surgery for SUI, SNM and percutaneous tibial nerve stimulation were only received by 21, 19 and 48 participants respectively.

Role of urodynamics in the decision-making process

In women with refractory OAB/MUI who underwent urodynamics, urodynamics did not show evidence of DO in 34% of cases, while 58% were diagnosed with DO or DOI and 8.0% with urodynamic MUI. Despite a baseline diagnosis of OAB or urgency-predominant MUI, 13% of participants had a diagnosis of urodynamic stress incontinence (USI) following urodynamics. However, only 20% of those with USI had a treatment decision for SUI surgery. No evidence of DO or USI was noted in 20% of cases.

Safety

In FUTURE, 21.4% of participants reported at least one adverse event, with slightly higher reporting in the CCA only arm; 122 (22.2%) versus 113 (20.5%), with urinary tract infections, need for prophylactic antibiotics and clean intermittent self-catheterisation having the highest rates.

As BoNT-A was the most comment treatment received, adverse events associated with BoNT-A (such as limb weakness and pain) were most often seen due to the higher number of participants receiving this treatment.

Health economic results

For the primary analysis, the mean costs in the urodynamics group were £463 higher (95% CI £48 to £877) compared with those in the CCA only group. This was principally due to the intervention itself and more clinic visits in this group. There was evidence of greater numbers of interventions for SUI in participants undergoing urodynamics, but all other effects are highly uncertain, and not statistically significant.

There is no clear evidence of differences in HRQoL (as measured by the EQ-5D-5L) at any time point. When modelled with imputation, a small but not statistically significant difference in QALYs of 0.011 (95% CI −0.044 to 0.065) was estimated in favour of the urodynamics group.

Based on the estimated incremental costs and QALYs of urodynamics (£463 and 0.011, respectively), the incremental cost-effectiveness ratio was £42,643 per QALY gained. The higher mean costs and QALYs therefore led to urodynamics not being cost-effective at a funding threshold of £20,000 per QALY gained, with only a 34% chance of it being cost-effective. However, this was sensitive to imputation, with the complete-case analysis showing a 67% chance of urodynamics being cost-effective. The subgroup analysis suggests larger health benefits for participants with an initial diagnosis of urgency-predominant MUI, which is associated with a 72% chance of cost-effectiveness.

Modelling the results over a lifetime horizon reduces the cost-effectiveness of urodynamics further. The primary, model-based economic analysis shows that urodynamics has a low probability of being cost effective at £20,000 per QALY gained (23.4%), producing modestly higher costs (£1380) and slightly lower QALYs (−0.002) per patient.

However, this analysis, together with a value of information analysis, should be updated once more information is available about the longer-term follow-up of participants recruited to FUTURE.

Qualitative

The qualitative interviews among clinicians highlighted that the main driver for the inclusion of urodynamics in their existing practice was its recommendation in guidelines and clinical judgement. For some, urodynamics was perceived to provide additional information to aid the treatment decision-making process, while others consider it of little additional value. Key components of the CCA include the bladder diary and history-taking, which clinicians acknowledged should be of high quality to offer maximum value to patient assessment. A clear message emerged that clinicians would like the option to include urodynamics only where it was deemed necessary but would be happy to consider not using it as a routine investigation dependent on the evidence. A desire for evidence-based guidance on the added value of urodynamics was expressed, which it was hoped would be provided through FUTURE.

Interviews among FUTURE participants highlighted a broad spectrum of opinion, reflecting individual personalities as well as the investigation itself. Participant views ranged from those who were prepared to undergo urodynamics as a means to provide direction for treatment for their enduring symptoms, through to those who were extremely worried about the discomfort and embarrassment associated with the procedure, to the point of refusing it. Given the refractory nature of the symptoms among the FUTURE participants, many were at a stage where they were 'willing to try anything'. The decision-making process is multifactorial though and not only based on views of the investigation itself. Guidance provided by the clinical team is a primary driver. Other factors include anecdotal experience, practicalities of urodynamics such as timescales, impact on work life and location of potential subsequent treatments. An element of 'validation' was described whereby a test suggests additional findings to guide treatment and makes women feel that their symptoms are taken seriously. Given the spectrum of perspectives, however, there was also articulated a sense of relief when avoidance of urodynamics was the outcome.

Conclusion

In participants with refractory OAB or urgency-predominant MUI, the participant-reported success rates following treatments in participants who undergo urodynamics and CCA are not superior to those who undergo CCA only up to 15-months follow-up. Significantly more women who undergo CCA only report earlier improvement in their symptoms. Urodynamics plus CCA is not cost-effective at a threshold of £20,000 per QALY gained.

Trial registration

This trial is registered as ISRCTN63268739.

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This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: 15/150/05) and is published in full in *Health Technology Assessment*; Vol. 29, No. 27. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

In 2016, the UK government's National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme funded the Female Urgency, Trial of Urodynamics as Routine Evaluation (FUTURE) project. This report describes the research. FUTURE was a superiority randomised controlled trial (RCT) evaluating the clinical and cost-effectiveness of invasive urodynamics in the management of refractory overactive bladder (OAB) symptoms in women.

Female urinary incontinence (UI), defined as the experience of involuntary urinary leakage,[2] is a highly prevalent condition of varying aetiology amongst women of all ages, and has a significant impact on women's lives.[3]

Types of urinary incontinence

Urinary incontinence can be characterised according to the incontinence symptoms. OAB is the symptom complex of urinary urgency (sudden desire to void that is difficult to defer) and is often associated with urgency urinary incontinence (UUI).[4] UUI is characterised by the involuntary loss of urine associated with feelings of urgency. Stress urinary incontinence (SUI) is characterised by the involuntary loss of urine associated with exertion, effort, sneezing or coughing. Mixed urinary incontinence (MUI) is identified by the presence of involuntary urine loss in association with symptoms of both SUI and UUI.[2]

Epidemiology of incontinence in women

The prevalence estimates of UI in the literature vary widely primarily due to the varying definition of UI used in these studies.[5] The Epidemiology of Incontinence in the County of Nord-Trøndelag (EPINCONT) survey uses the standard definition for UI (as above), and estimated an overall prevalence of UI in women of 30%, broadly increasing with age.[6]

The Leicestershire Medical Research Council (MRC) Incontinence Study showed a 21% overall prevalence of UI in women aged ≥ 40 years in the UK; UUI and MUI represented 11% and 36% of these women, respectively.[7] The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) study reported a similar UUI prevalence rate of 13.3% for men and 30.3% for women in the USA.[8] In 2016, Komeso reported a large epidemiological study showing that the prevalence of UI increases with age; this was most apparent for UUI and MUI: the odds of occurrence of UUI were two- and ninefold increased in the 7th and 10th decades, compared with the 6th decade [odds ratio (OR) 2.18 (95% confidence interval (CI) 1.50 to 3.15) and OR 9.19 (95% CI 5.56 to 15.20)], respectively.[9] The prevalence of MUI also significantly increased in the 8th to 10th decades (both $p \leq 0.005$) but, interestingly, the prevalence of SUI did not seem to increase with age in this study. Estimation models predict that the worldwide number of adults aged ≥ 20 years with UUI or MUI was 103 million in 2008, with a projected increase to 127 million in 2018.[10] We can therefore conclude that the prevalence of OAB/MUI is likely to increase in the years to come, especially given the ageing population in the UK. The EPINCONT data estimate an annual incidence and remission rate of 1.7% and 3.1%, respectively.[11] A similar study reported annual incidence and remission rates of 1.3% and 2.1%, respectively.[12]

The burden of incontinence

Urinary incontinence significantly impacts both the patient and society as it brings significant personal, sexual and economic burdens.

Personal impact

Urinary incontinence is an important source of personal embarrassment, and the stigma surrounding adult UI is a significant barrier to seeking appropriate healthcare support.[13] The private and personal nature of UI can undoubtedly impact overall mental health. Indeed, studies have identified an increased psychological burden and increased likelihood of depression in UI sufferers.[14–16] UI is second only to dementia as a reason for placing elderly women in residential or nursing homes.[17]

Overactive bladder and UUI have been shown to have a negative impact on a woman's physical, social and psychological well-being, leading to low self-esteem, embarrassment and low productivity of working women. Women reported avoiding employment because of fear of embarrassing situations; 60% reported social isolation, avoiding leaving their home and 50% reported reduction or avoidance of sexual activity.[7,12,18] Norton *et al.* reported that 50% of women were avoiding sexual activity due to fear of UI, while 25–50% of women had difficulty with orgasm or dyspareunia, leading to negative impact on personal relationships for some women.[18]

Personal and societal economic impact

Urinary incontinence has significant cost implications for the health resources in the UK, with an estimated total annual cost to the NHS of £301 million or 0.3% of the total NHS budget in 2009.[19] Furthermore, UI can incur significant personal costs. Patient-purchased management devices, such as absorptive pads, can create significant economic burden, which was estimated at £230 million in the UK or £290 per woman per year at 2000 prices.[20] One US study reported $750 per year in personal costs.[21]

A large multinational study estimated the health-related costs for management of OAB and UUI in 2005 at approximately €7.0 billion across six countries: Sweden, Canada, Spain, Germany, Italy and the UK.[10]

Pathophysiology of overactive bladder

The standardised definition of OAB according to the International Continence Society (ICS) is 'urgency, with or without UUI, usually in the presence of frequency and nocturia, in the absence of any other pathology'.[4] It is important to highlight that OAB is not synonymous with detrusor overactivity (DO) assessed via urodynamics although the prevalence of DO increases in those with UI from 44% to 69%. There is a good correlation between UUI (wet OAB) and DO on urodynamic investigations.[22] It is important to understand that DO is a urodynamic diagnosis, and that the observation of involuntary contractions must be correlated with the patients' symptoms during the urodynamic test and with their presenting symptoms. However, asymptomatic DO can also be diagnosed. Idiopathic DO is the most common type of DO when there is no defined cause such as inflammatory factors,[23] or underlying neurogenic pathology.[24]

Clinical assessment of urinary incontinence in women

Norton *et al.* showed that 25% of women waited more than 5 years before seeking help because of embarrassment or fear of surgery.[18] Data from National Institute for Health and Care Excellence (NICE) indicate that the standard benchmark rate for a referral to a UI service for women in the UK is 0.8% (800 per 100,000 adult female/year).[25]

There are several essential elements for the comprehensive clinical assessment (CCA) that can together form a platform for diagnosis for women with lower urinary tract symptoms (LUTS) and UI. CCA includes (1) history-taking using structured interviews, validated questionnaires for symptom severity and impact on health-related quality of life (HRQoL) and sexual function, (2) bladder diaries and (3) non-invasive tests such as cough stress test (CST), pad tests, uroflowmetry and bladder scan, urinalysis, and measurement of body mass index (BMI).

Structured interview and validated questionnaires

Initial patient interview is vital in cases of LUTS and UI. It can detect risk factors for various types of LUTS such as age, menopause, parity, previous pelvic floor surgery, chronic cough, chronic constipation, cardiac failure or neurological diseases. Moreover, the obstetric history and concomitant drug history (such as sedatives, diuretics or anticholinergics) are important for assessment of UI and planning future management. It is also important to classify the predominant or most bothersome type of UI to the patient (OAB/UUI vs. SUI). The interview can establish the severity of the condition, including the number of incontinence pads used and previous treatments tried. NICE guideline NG123 recommends: 'At the initial clinical assessment, categorise the woman's UI as SUI, MUI or UUI/OAB. Start initial treatment on this basis. In MUI, direct treatment towards the predominant symptom'.[3]

Such interviews can be performed with the aid of integrated validated questionnaires completed by the patients during or prior to the interview. This can help to explore all elements of LUTS, including the storage phase, voiding phase and UI.

Several validated questionnaires exist to assess the severity, type and HRQoL impact of UI. For instance, the International Consultation on Incontinence Questionnaire (ICIQ), with the full detailed ICIQ-FLUTS module, and the short form (SF), ICIQ-UI-SF, and the HRQoL questionnaire, ICIQ-LUTSQoL.[26] Other tools include the urinary distress inventory-6,[27] impact of incontinence questionnaire-7 (IIQ-7),[28] and the King's Health Questionnaire (KHQ).[29] Sexual function can similarly be assessed using validated questionnaires. One widely used example is the SF of the pelvic organ prolapse / urinary incontinence sexual questionnaire 12 (PISQ-12).[30] To represent sexually inactive patients, the International Urogynaecological Association (IUGA) developed the PISQ-IUGA revised (PISQ-IR).[31]

Examination

Following the patient interview, physical examination is essential to formulate the diagnosis. In addition to an abdominal examination, gynaecological examination can aid in detecting anatomical defects, possible pelvic masses, vaginal atrophy, urogenital fistulae, prolapse, as well as assessment of the pelvic floor during increased intra-abdominal pressure.[32]

The CST is a simple bedside test often performed during the examination with a comfortably full bladder, either in the lithotomy position or upright, where the patient is asked to cough or perform the Valsalva manoeuvre. Leakage of urine during the period of increased intra-abdominal pressure points towards a diagnosis of SUI.[2] The mobility of the urethra can also be assessed visually at the same time.

Assessment tools

Frequency/volume charts or bladder diaries can help provide clinical information on urinary symptoms and habits, and symptom severity.[2] Three-day bladder diaries offer reduced patient burden[33] and correlate well with UI episodes measured over 4 subsequent days (correlation coefficient = 0.887).[34] NICE recommends a 3-day bladder diary in the initial assessment of women with UI.[3]

Bladder scans are helpful non-invasive bedside tests to assess the post-void residual (PVR) urine volumes for women with UI and are recommended by NICE as part of the CCA.[3]

Integrating all the above elements of a CCA can form a platform for diagnosis of women with LUTS and UI. However, the bladder has been traditionally described as an unreliable witness. Several authors in the past believed the real pathophysiology for LUTS might be difficult to interpret based on symptoms alone. This sentiment is primarily due to the frequent lack of agreement between the clinical diagnosis and diagnosis based on invasive investigations (i.e. urodynamics). Interestingly, the current literature lacks any robust evidence to show that treatments of UI based on urodynamic findings are associated with better outcomes compared to those based on CCA alone.[35]

Urodynamic assessment of urinary incontinence in women

Urodynamic assessment is a combination of non-invasive measures (uroflowmetry) and invasive measures (cystometry).

The role of urodynamic testing in uncomplicated UI is debatable, with several trials suggesting no benefit over office-based, non-invasive, preoperative assessment.[36–38] However, urodynamic assessment may be beneficial where the clinical features are unclear.[39]

At the time of the study design, in women with OAB/UUI and after failure of conservative and medical treatment, NICE recommended 'urodynamic' investigation to confirm the diagnosis of DO in women with urgency-predominant UI.[25] NICE recommends uroflowmetry and multichannel filling and voiding cystometry.

Uroflowmetry

Uroflowmetry is a non-invasive method to measure urinary flow rate, and the total volume of voided urine. The primary measurements for female patients are the maximum and average flow rates (Q-max and Q-avg, respectively), the voiding pattern, the PVR and the voided volumes.[40] Such measurements aid in assessing patients with potential voiding dysfunction.[41]

Invasive urodynamic tests (multichannel filling cystometry and voiding pressure flow)

The test involves the insertion of one or two small catheters less than size 8 Fr into the bladder and another one into the vagina or the rectum (the latter is preferrable). The rationale for urodynamics is to reproduce the women's symptoms and to identify the underlying pathology. The bladder is slowly filled with saline, and the bladder pressure is measured. At the same time, abdominal pressure is measured, since the bladder is an abdominal organ. The difference between these pressures is calculated throughout the test by a computer and plotted as the 'detrusor pressure', which indicates whether the bladder is contracting and generating pressure. The patient is asked to report her sensations related to bladder filling. Key abnormal observations that might be seen during the filling cystometry include bladder contractions (referred to as DO), steady climbing detrusor pressure (low compliance) and urinary leakage when there is a rise in abdominal pressure (USI). When the patient experiences a strong desire to pass urine, she is said to have reached functional cystometric capacity, and permission to pass urine is given. This is the start of the pressure flow study, which looks at voiding function. Key abnormal observations that might be seen during the pressure flow study include a slow flow rate despite high detrusor pressure, which may indicate bladder outlet obstruction. Alternatively, slow flow may be due to weak bladder contraction, referred to as detrusor underactivity.

During bladder filling, DO is particularly relevant to the current study; these are uninhibited bladder contractions, which hinder effective urine storage, and are frequently associated with urgency and/or UUI. Urodynamic stress incontinence (USI) may also be seen, and if USI and DO incontinence (DOI) are both present, the woman is diagnosed with urodynamic MUI. Urodynamics can also identify other pathologies, for example bladder outflow obstruction or detrusor underactivity during voiding, which may influence the choice of therapy.

Conservative and non-surgical management of overactive bladder

Lifestyle modifications

Weight loss in high-BMI individuals has been shown to reduce the severity of UI symptoms.[42,43] NICE recommends weight loss if BMI is more than 30, modification of fluid intake to avoid excessive or low fluid intake and a trial of caffeine reduction.

Other lifestyle modifications include smoking cessation and reduction of high-intensity exercise, although evidence is less clear for such modifications.[32]

Pelvic floor strengthening

Pelvic floor exercises

Pelvic floor muscle training (PFMT) is widely used to treat UI and focuses on strengthening the pelvic floor muscles (PFM) through exercises. A 2018 Cochrane review found that PFMT significantly improves female UI symptoms [risk ratio (RR) 6.33 (95% CI 3.88 to 10.33); 3 trials, 242 women; moderate-quality evidence].[44]

Biofeedback

Pelvic floor muscle training can be combined with patient biofeedback to relay information regarding PFM contraction back to the patient. This is thought to help maintain awareness of PFM function during exercises, for example through vaginal pressure measurements.[45] However, a recent RCT (n = 600) suggests that biofeedback provides no benefit over regular PFMT [mean difference in ICIQ-UI-SF at 24 months −0.09 (95% CI −0.92 to 0.75); p = 0.84].[46]

Behavioural therapy

NG123 recommends a minimum of 6 weeks bladder retraining as first-line treatment for women with OAB/UUI.[3]

Pharmacological treatment

In clinical practice, anticholinergic or antimuscarinic medications are usually considered as first-line treatment in women with OAB and UUI alongside bladder retraining and PFMT. There are several types of anticholinergic drugs used in clinical practice, predominantly oral medications (oxybutynin, tolterodine, solifenacin, darifenacin, trospium, fesoteoridne and propiverine). Common side effects include constipation, dry eyes and dry mouth. The long-term effect of using anticholinergic drugs on cognitive function is unknown. There are concerns about the long-term use of anticholinergic drugs and the impact on the cognitive function especially in elderly patients with multiple morbidity as anticholinergic load burden can be highest in them.[47]

Standard clinical practice based on NICE recommendations is that women with OAB/UUI are started on one of the above medications as part of the conservative management plan, after a full review of physical and mental status and comorbidities, as well other medications that the patient may be taking, with special consideration of the anticholinergic load. NICE recommends review of treatment outcome in 4–6 weeks and to try an alternative anticholinergic medication if ineffective or poorly tolerated. Transdermal oxybutynin can be an option in women with intolerance to oral medications.

Mirabegron and vibegron are another class of oral medication that can be used in women with OAB/UUI. They are beta-3 adrenergic agonists and facilitate urine storage, hence are used in medical treatment of OAB/UUI if anticholinergic medications are not tolerated or contraindicated. In clinical practice, clinicians would recommend a trial of a minimum of two or three types of pharmacological treatment before proceeding to invasive treatments.

National Institute for Health and Care Excellence Guideline NG123 recommends initial conservative treatment, which includes lifestyle modifications, bladder training and PFMT and pharmacological therapy (anticholinergics and/or beta-3 agonist).[3] However, these measures are unsuccessful for approximately 25–40% of women. These women are then considered to have refractory OAB.[48] For these women, and at the time of the study design, NICE recommended ‘urodynamic’ investigation to confirm the diagnosis of DO, before proceeding to invasive treatments such as a botulinum toxin injection A (BoNT-A) or sacral neuromodulation (SNM).[25]

Invasive treatments for refractory overactive bladder

National Institute for Health and Care Excellence recommend injection of BoNT-A into the bladder wall or SNM as the treatments for women with refractory OAB following failure of conservative and medical treatment and a confirmation of urodynamic diagnosis of DO.[25]

Botulinum toxin injection treatment

This is the injection of BoNT-A into the bladder wall during cystoscopy (rigid or flexible), under general or more commonly local anaesthesia. The treatment, if successful, is usually repeated every 6–12 months.

In women with refractory OAB and associated DO on urodynamics, Brubaker *et al.* showed that approximately 60% of the women who received BoNT-A had a positive clinical response based on the Patient Global Impression of Improvement scale (PGI-I).[49] Secondary analyses performed in two RCTs of BoNT-A versus placebo suggested that successful treatment outcomes did not appear to be related to the preoperative urodynamic diagnosis of DO.[50,51] Chapple *et al.* (2013), in a double-blind, placebo-controlled RCT, showed that BoNT-A significantly improves all symptoms of refractory OAB and HRQoL; there was no impact of the preoperative diagnosis of DO on the treatment outcomes.[51] Similarly, Rovner *et al.* (2011) in a placebo-controlled RCT showed that 57% of the patients were satisfied with their treatment (compared to 19% placebo) at 3 months following BoNT-A treatment, irrespective of the presence of DO on urodynamics.[50] BoNT-A is now licensed in the UK for the treatment of refractory OAB/UUI symptoms without the need for preoperative urodynamics.

In a recent observational study embedded within the Bladder Ultrasound Study (BUS), 666 women with non-refractory OAB underwent urodynamics; the results suggested that clinicians and patients appeared to be guided in part by the urodynamic diagnosis in selecting treatment options.[52] Several confounding influences were identified, such as natural fluctuation of disease state, regression to the mean and Hawthorne effects. The economic modelling within the BUS study suggested that urodynamics can be a cost-effective diagnostic strategy for women with predominant symptoms of OAB.[52] However, this was based on fewer women undergoing invasive treatment in the urodynamics group rather than achieving better outcomes. The authors reported significant cost savings in the urodynamics group associated with a small reduction in clinical effectiveness. It is important to highlight that the BUS study assessed a different cohort of women with significantly milder OAB symptoms and therefore the results could not be generalised to women with refractory OAB.[52]

Sacral neuromodulation

The principle of SNM is that electrical stimulation of the sacral reflex pathway will inhibit the reflex behaviour of the bladder.[53] SNM is a two-stage procedure; stage one is a test phase using either a temporary or permanent lead, connected to an external stimulator, while the second stage involves the placement of a subcutaneous implantable pulse generator (IPG; permanent battery implant). If a patient reports at least 50% improvement of the refractory OAB symptoms during the test phase, as recorded in the bladder diaries, they are offered the permanent implant. SNM has a unique advantage, as patient outcomes are assessed before a commitment is made to the full implant.

Three RCTs comparing SNM to placebo showed that 52% of patients were dry at 18 months and a further 24% reported at least 50% reduction in leakage episodes; at 3 years, 46% were dry and 13% improved.[53–55] In one RCT, patients with urgency and increased frequency showed improvements in several short form-36 (SF-36) domains in the active treatment group (n = 51; 90% women) at 6 months' follow-up.[55] NICE concluded that following SNM, up to two-thirds of patients achieve continence or substantial improvement in symptoms, with the beneficial effects lasting for up to 3–5 years after implantation.[25] Around one-third of patients may require re-operation, most often due to pain at the implant site, infection, or the need for adjustment and modification of the lead. Urodynamic investigation is considered a standard practice prior to SNM treatment. However, one recent observational study reported that pre-operative diagnosis of DO was not a prerequisite selection criterion for SNM.[56]

Sequence of treatment in women with refractory overactive bladder

The best sequence of interventions for women with refractory OAB is not known.

In 2013, NICE CG171 included a health economic evaluation which suggested that, in the short term, BoNT-A was a cost-effective intervention both in comparison with no active treatment and also in comparison with SNM.[25] On the balance of evidence, NICE justified the recommendation to offer BoNT-A as first intervention to women with refractory OAB and DO. They recommended SNM for women who are unable to catheterise or have a cultural or ethical objection to catheterisation, or those with persistent symptoms following BoNT-A treatment.

Interestingly, evidence from one recent study highlighted that 61% of women receiving BoNT-A discontinued their treatment at 3 years while 64% discontinued at 5 years.[57] Most recently, Marcelissen *et al.* showed that only 30% of patients initiated on BoNT-A treatment were still on treatment at a minimum follow-up of 5 years; most patients who discontinued treatment (98%) did so after the after the first or second injection.[58] In an economic model comparing SNM

with BoNT-A over a 5-year period with a societal perspective, Leong *et al.* reported a greater gain in quality-adjusted life-year (QALYs) and a greater associated cost saving when patients were initiated on SNM treatment.[59] As the QALY gain from BoNT-A injection was lower due to the loss of effect with re-injections over time, SNM was demonstrated to become cost-effective after 5 years compared with BoNT-A, with an incremental cost-effectiveness ratio (ICER) of 27,991 euros, which is within the accepted NICE threshold of £20,000–£30,000.

Accordingly, practice in the UK can vary and usually relies on the treatment options available within units. The brief survey of the potential collaborating sites for the FUTURE trial, at the time of the trial design, suggests a considerable number of units and surgeons offer BoNT-A treatment for women with refractory OAB with and without urodynamic evidence of DO. In addition, in tertiary units with SNM readily available, surgeons tend to offer women with confirmed DO the choice between BoNT-A and the SNM test procedure after discussion by the local multidisciplinary team (MDT). Some surgeons indicated that they favour SNM in younger patients and/or those with associated voiding dysfunction or faecal incontinence.

In summary, the current evidence highlights the uncertainties and the timely need for a robust RCT to address this important research question which was prioritised by the NICE guideline CG171 research recommendations: 'Further research is needed to answer the question of whether the use of invasive urodynamics, prior to initial or subsequent treatments, affects the outcomes and cost-effectiveness of interventions in women with UI or OAB'.[25]

Rationale for the Female Urgency, Trial of Urodynamics as Routine Evaluations trial

Research question

Does routine urodynamic investigation in addition to CCA improve participant-reported outcomes following treatment, compared to CCA only, in women with refractory OAB symptoms and is it cost-effective?

Rationale

National Institute for Health and Care Excellence recommends urodynamic investigation to confirm the diagnosis of DO in women with refractory OAB before proceeding to invasive treatment.[25]

Refractory OAB is defined as OAB symptoms that are refractory to conservative and medical treatment including bladder retraining and PFMT and a minimum of two types of pharmacological therapy (anticholinergics and/or beta-3 agonist).

For clinicians, urodynamics is traditionally considered to inform the counselling of women on the chances of success of subsequent treatments. However, in women with refractory OAB, urodynamics fails to show evidence of DO in up to 45%.[60] The accuracy of urodynamics relies on well-calibrated equipment, the experience of investigators and their objective interpretation of a number of subjective parameters. Hence the standardisation of the test is difficult and is affected by the wide variation in staff practice and type of equipment used.[61] These factors raise a valid debate on the clinical and cost-effectiveness of urodynamics and whether it actually improves the outcomes following subsequent treatments compared to treatment guided by CCA only.

From the patients' perspective, many describe urodynamics as an invasive and embarrassing investigation, associated with an element of emotional distress.[62,63] Urodynamics is also associated with a risk of discomfort and urinary tract infection (UTI).[52] However, the majority of women find it acceptable if it will ultimately improve their outcomes post treatment.[52,64-66]

Unfortunately, the urodynamics test may not replicate the patients' symptoms in their day-to-day lives, which questions the validity of the treatment options offered based on its results.

For policy-makers, inevitably urodynamics is costly to the NHS, including purchase of equipment and disposables, and the need for specialist staff. The urodynamics tariff was £256/patient at the time of the trial design. Policy-makers are faced with the current pressure on health resources in the UK; therefore, there is a pressing need to direct resources towards evidence-based interventions that are proven to positively improve treatment outcomes.

Urodynamics is a test that has been embedded in clinical practice without robust evidence of its clinical or cost-effectiveness.[67] Robust evidence shows urodynamics to have no impact on participant-reported outcomes following conservative treatment of UI[68] and for those undergoing surgical treatment for symptoms of pure SUI.[37] Accordingly, NICE CG171 has prioritised research to assess the clinical and cost effectiveness of urodynamics in treatment of refractory OAB.[25] The outcome of the FUTURE trial will inform patients, clinicians and policy-makers whether routine urodynamic investigation improves the treatment outcomes in women with refractory OAB and whether it is cost-effective.

Chapter 2 Methods and practical arrangements

Trial design

Female Urgency, Trial of Urodynamics as Routine Evaluations was a pragmatic, parallel-group, multicentre, superiority RCT designed to compare the clinical and cost-effectiveness of routine urodynamics plus CCA versus CCA only in the management of women with refractory OAB symptoms.

A qualitative component was embedded within the trial design to evaluate patients' attitudes to, and experiences of, invasive urodynamics, and clinicians' views on the influence of urodynamics on their decision-making for diagnosis and subsequent treatments.

Further details of the trial design have been described previously[1] and are represented in *Figure 1*. All trial case report forms (CRFs) and participant-completed questionnaires are included in Project Documents: Trial Paperwork-CRFs and Project Documents: Trial Paperwork-Questionnaires.

Study population

Women aged ≥ 18 years with refractory OAB or urgency-predominant MUI were included if they:

- had failed conservative management (as per NICE guidelines, e.g. PFMT/bladder retraining)
- had failed or have not tolerated pharmacological treatment (at least two different drugs) unless contraindicated
- were being considered for invasive treatment.

Women were excluded from trial entry if any of the following criteria were met: predominant SUI symptoms; previous urodynamics in the last 12 months; current pelvic malignancy or clinically significant pelvic mass; bladder pain syndrome; neurogenic bladder (e.g. Parkinson's disease, spinal injuries, etc.); urogenital fistulae; previous treatment with BoNT-A or SNM for UI; previous pelvic radiotherapy; prolapse beyond introitus; pregnant or planning pregnancy; recurrent UTI where a significant pathology has not been excluded; and inability to give informed consent.

Consent to participate

Women with OAB or urgency-predominant MUI who fulfilled the inclusion criteria were identified at outpatient clinics or from urodynamic/outpatient waiting lists. Participant identification centres were also used to identify potential participants. Women were given/sent the patient information leaflet (PIL) (see www.fundingawards.nihr.ac.uk/award/15/150/05) and had the opportunity to discuss the study with the local clinical team, research nurse and, if appropriate, their general practitioner (GP), family and friends. Women could make the decision to participate during their initial consultation, during a subsequent hospital visit or at home. Written informed consent was obtained from all participants prior to trial entry (see www.fundingawards.nihr.ac.uk/award/15/150/05).

Health technologies being compared

Women were randomised to one of the following interventions:

1. Urodynamics plus CCA
2. CCA only.

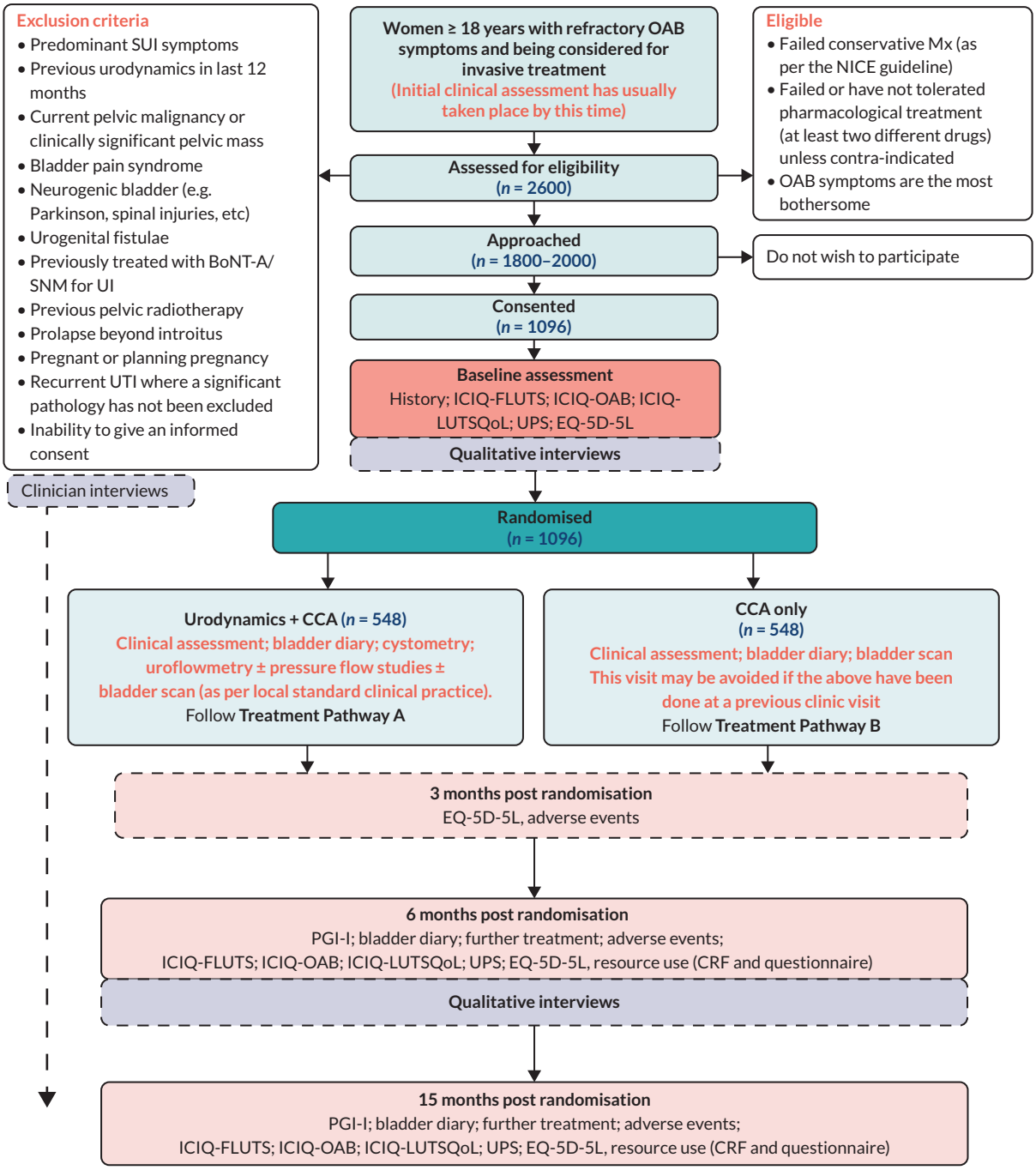

FIGURE 1 Flow diagram. EQ-5D-5L, EuroQol-5 Dimensions, five-level version

Treatment allocation

Eligible and consenting women were randomised by the research nurses to one of the two treatment arms in a 1 : 1 allocation ratio using the randomisation application at the trial office at the Centre for Healthcare Randomised Trials (CHaRT). The randomisation application was available as a web-based application and used stratified random permuted blocks with (1) site and (2) diagnosis of OAB versus urgency-predominant MUI used as stratum.

Blinding

Baseline data were reported by participants before randomisation using self-completed questionnaires. Participants, clinical staff and the central trial team could not be blinded to the allocated procedure because of the nature of the interventions.

Intervention: Urodynamics plus comprehensive clinical assessment

This was a comprehensive invasive and non-invasive assessment of women with urinary symptoms and included:

- cystometry
- free uroflowmetry with/without pressure flow studies with/without bladder scan
- detailed medical history (assessment of urinary symptoms (storage, filling and incontinence symptoms and the most bothersome urinary symptoms), previous investigations and/or treatments (conservative, pharmacological and/or surgical) for UI and OAB and past medical or surgical history of relevance)
- clinical examination including assessment for SUI, pelvic organ prolapse and pelvic masses and other pelvic pathology
- bladder diary for 3 days to assess daytime frequency, nocturia, urgency and UUI episodes; a minimum of 24 hours completed diary was accepted as a valid diary. Diary completed at a previous clinic visit within the last 3 months was also accepted.

Standardisation of intervention

To be assured of good quality measurements and accurate urodynamic data recording, a guide for standardising urodynamics best practice (see www.fundingawards.nihr.ac.uk/award/15/150/05) was developed in conformity with the ICS Good Urodynamics Practices.[69]

Prior to performing the first randomised urodynamics test, collaborating units were required to undertake urodynamic machine calibration checks and submit two anonymous urodynamics traces with their reports for central reading and review by a panel of experts within the FUTURE trial team. Feedback was given to sites with any required improvement steps.

During the course of the study collaborating units were required to submit copies of the urodynamics trace/report for all participants randomised to the urodynamics arm for archiving purposes. Random central checks of traces/reports were undertaken after 10 traces/reports were submitted per unit (5 for low-recruiting units) for quality assurance (QA). When required, one-to-one feedback was provided, and closer monitoring (random central checks after five traces/reports) undertaken (further details are described in *Chapter 7*).

Treatment pathway following intervention

The treatment pathway following the intervention was guided by the urodynamics diagnosis and was in line with NICE guidelines[25] which recommended BoNT-A as the first line treatment for refractory OAB (see www.fundingawards.nihr.ac.uk/award/15/150/05). NICE CG171 recommended BoNT-A at 200 units; however, since its publication, further evidence confirmed the efficacy of BoNT-A treatment at the lower dose of 100 units with fewer adverse events (AEs).[70] Subsequent NICE guidelines (NG123) also recommended initial treatment with 100 units.[3]

NICE CG171 further recommended SNM treatment for patients who were unable or unwilling to perform clean intermittent self-catheterisation (CISC) or following unsuccessful BoNT-A treatment pending a local MDT discussion.[25]

However, in view of the lack of robust evidence on the best sequence of treatments in women with refractory OAB, participants with DO on urodynamics within FUTURE, could be offered either BoNT-A (100 units) or the SNM test; the decision was discussed in the local MDT or as per local standard best practice. This approach varied between units depending on their local clinical practice and the availability of treatments. Participants with other diagnoses on urodynamics were offered the appropriate treatments.

Depending on the clinical outcome of initial treatment, participants with persistent or de novo UI symptoms were offered further urodynamic tests and/or further/repeat treatment as appropriate (see www.fundingawards.nihr.ac.uk/award/15/150/05).

Intervention: comprehensive clinical assessment only

This was a non-invasive comprehensive intervention which included a detailed medical history, clinical examination, bladder diary (as outlined above) and PVR urine volume using ultrasound bladder scanning with/without non-invasive free uroflowmetry.

Treatment pathway following intervention

The treatment pathway following the intervention was guided by the clinical diagnosis and non-invasive tests (see www.fundingawards.nihr.ac.uk/award/15/150/05). As discussed above, participants with clinically diagnosed refractory OAB or urgency-predominant MUI could be offered either BoNT-A or the SNM test. Participants with other clinical diagnoses (such as overflow incontinence or SUI predominant MUI) were offered other appropriate treatments such as CISC, SUI surgery or other medical/conservative treatments as per local standard best practice, including MDT discussions.

Depending on the clinical outcome of initial treatment, participants with persistent or de novo UI symptoms were offered urodynamics and treatment accordingly or repeat/further treatment according to the CCA (see www.fundingawards.nihr.ac.uk/award/15/150/05).

Data collection

Participant-reported outcomes were assessed by self-completed questionnaires at baseline, 3, 6 and 15 months post randomisation (*Table 1*). A self-completed 3-day bladder diary was also completed at baseline, 6 and 15 months post randomisation. Up to three reminders were sent to participants by post, e-mail, phone or text message, taking into account any preferences they had for mode of communication.

Intervention data were collected on CRFs. For both arms this included data from the detailed medical history and clinical examination, as well as a baseline clinical diagnosis of OAB or urgency-predominant MUI.

For the urodynamics plus CCA arm, data were also collected from the urodynamics test, including urodynamic diagnosis, voiding assessment on free uroflowmetry and pressure flow studies (if the latter were performed) and maximum urethral closure pressure on urethral pressure profile (if performed). For the CCA arm, data were collected on the PVR urine volume using ultrasound bladder scanning (and/or non-invasive free uroflowmetry if performed).

A case-note review was also conducted by the local research team at 6 and 15 months post randomisation to collect information on treatments received, any subsequent and relevant outpatient clinic visits, investigations and treatments and AEs.

Implications of coronavirus disease-19 on data collection

The primary aim of the FUTURE trial was to assess participant-reported improvement in symptoms following treatment for OAB. However, as routine NHS treatments were initially suspended due to the coronavirus disease-19 (COVID-19) pandemic, some participants received the 15-month post-randomisation questionnaires before receiving their treatment.

Therefore, participants whose treatment had been delayed by the pandemic received an additional questionnaire at 24 months post randomisation. The questionnaire contained the same suite of questions as the 15-month post-randomisation questionnaire and followed the same reminder system. A case-note review was also conducted for these participants at 24 months post randomisation.

TABLE 1 Source and timing of outcome measures

Outcome measure	Source	Timing			
			Post randomisation (months)		
		Baseline	3	6	15
Treatment success PGI-I	PQ		✓	✓	✓
Generic health status	PQ	✓	✓	✓	✓
EuroQol-5 Dimensions, five-level version					
Condition-specific quality of life	PQ	✓		✓	✓
ICIQ-LUTSQoL					
Urinary symptoms	PQ	✓	✓	✓	✓
ICIQ-OAB					
ICIQ-FLUTS					
UPS					
Urgency and UUI episodes (3-day bladder diary)	PQ	✓		✓	✓
Bladder scan	CRF	✓			
Interventions received	CRF, PQ		✓	✓	✓
AE	CRF, PQ		✓	✓	✓
NHS primary and secondary healthcare use	CRF, PQ	✓		✓	✓
Participant resource use	PQ	✓		✓	✓

Where a participant completed a 24-month questionnaire in addition to a 15-month questionnaire, the participant-reported outcomes at the final time point were those from the 24-month questionnaire. Participants who received but did not complete a 24-month questionnaire had their 15-month questionnaire used as the final time point; for all other participants the final time point reported was their 15-month questionnaire. Statistical modelling of repeated measures on a participant used the 3-month, 6-month and final time points where the relevant outcomes were collected. All completed questionnaires were used to identify AEs, complications and treatments received by a participant.

Primary clinical outcome measure

The primary outcome measure was participant-reported success at the last follow-up time point (either 15 or 24 months post randomisation) as measured by the PGI-I.

The PGI-I is a validated single-item questionnaire designed to assess a participant's impression of changes in their urinary symptoms. The PGI-I asks the participant to best describe their urinary symptoms, compared with how they were before the trial intervention, on a seven-point scale scored as: (1) 'very much improved', (2) 'much improved', (3) 'improved', (4) 'same', (5) 'worse', (6) 'much worse' or (7) 'very much worse'. In FUTURE, 'Success' was defined as responses of 'very much improved' or 'much improved'.

Secondary clinical outcome measures

Other outcome measures included:

- a less strict definition of success at the last follow-up time point where success was defined as responses of 'very much improved', 'much improved' or 'improved'
- participant-reported success in the first 2 months following BoNT-A (for women who received BoNT-A only)
- proportion of women receiving invasive treatment at 6, 15 and 24 months post randomisation
- OAB symptoms measured by the ICIQ-OAB and the urgency perception scale (UPS)
- urgency and UUI episodes measured using the 3-day bladder diary
- other urinary symptoms measured using the three domains of the ICIQ-FLUTS (filling, voiding and incontinence) and the bladder diary
- general HRQoL status measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) and condition-specific ICIQ-LUTSQoL assessment tools
- AEs.

Economic outcome measures

Hospital resource use was gathered at study visits by reviewing medical records, while primary care and non-NHS costs were captured by patient questionnaires. The EQ-5D-5L, as described above, was used to calculate QALYs for the cost-effectiveness analysis. Further details are given in *Chapter 5*.

Safety reporting

In FUTURE, only AEs and serious adverse events (SAEs) related to the trial interventions were recorded. A SAE was defined as any AE that: resulted in death; was life threatening; resulted in persistent or significant disability or incapacity; required hospitalisation or prolongation of existing hospitalisation; or was otherwise considered medically significant by the investigator.

All AEs and SAEs meeting the criteria for recording within the trial were recorded from the time a participant consented to join the trial until the end of their follow-up period. Every follow-up visit and questionnaire asked about AEs/SAEs. In addition, open-ended and non-leading verbal questioning of the participant was used to enquire about AE/SAE occurrence.

Depending on severity, when an AE/SAE that met the criteria for recording within the FUTURE trial occurred, it was the responsibility of the local principal investigator (PI) (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The PI or delegate recorded all relevant information in the CRF (and on the SAE form if required).

Principal investigator or delegates were responsible for notifying the trial office of any SAEs that required to be recorded in line with the FUTURE trial protocol. If a SAE was recorded on a participant questionnaire, the trial office liaised with the relevant research site to obtain further information.

When a SAE form was uploaded onto the trial website, the Trial Manager was automatically notified. If, in the opinion of the local PI and/or the chief investigator, the event was confirmed as being serious, related and unexpected, the chief investigator or trial manager would notify the trial co-sponsors University of Aberdeen/NHS Grampian (NHSG) within 24 hours of receiving the signed SAE notification. The sponsor would then provide an assessment of the SAE. The sponsor could not downgrade an assessment from the PI or chief investigator. Any disparity would be resolved by further discussion between the parties.

The chief investigator or delegate would also report any related and unexpected SAEs to the Research Ethics Committee (REC) within 15 days of the chief investigator becoming aware of the event.

Sample size

A survey of the collaborating units showed that in clinical practice most women with refractory OAB are initiated on BoNT-A treatment (60–70%) compared to SNM (15–20%) or other/no treatments (10–25%). In addition, Rovner *et al.* and Chapple *et al.* both showed a success rate of around 60% in women with refractory OAB without the urodynamics diagnosis of DO.[50,51] These two studies defined success differently: Chapple *et al.* assessed participant-reported success at 12 weeks following injection of 100 units BoNT-A and defined success as 'greatly improved' or 'improved';[51] Rovner *et al.* used a dose of 300 units and defined success as no UUI episodes recorded in a 7-day diary recorded at 12 weeks post treatment.[50]

A consensus was also established amongst clinicians and their patient and public involvement groups (PPI) that for urodynamics to be worthwhile, it would need to demonstrate a minimum of 10% superiority over CCA only. For 90% power and a 5% level of significance, 986 participants (493/group) were needed using a chi-squared test with continuity correction,[71,72] rising to 1096 (or 548/group) to allow for 10% attrition at 15 months post randomisation.

Statistical analysis

Analyses were conducted using Stata version 17 (StataCorp LP, College Station, TX, USA).[73] Primary and secondary outcomes were compared using generalised linear models (GLMs), with adjustment for the minimisation covariates (site and diagnosis of OAB vs. urgency-predominant MUI).

The statistical analysis of the primary outcome was based on the intention-to-treat (ITT) principle, analysing women in the groups to which they were randomised. A per protocol analysis was also included as a secondary supporting analysis (see *Report Supplementary Material 1*).

The primary outcome was participant-reported success as measured by the PGI-I at the last follow-up time point. For the primary analysis, the PGI-I responses were dichotomised to 'success' defined as 'very much improved' or 'much improved'. A repeated-measures mixed-effects logistic regression was used, including the 6-month measurement to increase the power to estimate the treatment effect at the last follow-up time point.

Secondary outcomes were analysed using the appropriate linear model. For example, the less strict definition of success was analysed using a repeated-measures mixed-effects logistic regression in the same way as the primary outcome was analysed. The proportion of women receiving invasive treatment was analysed using a logistic regression. Continuous outcomes such as ICIQ-FLUTS and EQ-5D-5L were analysed using a repeated-measures mixed-effects linear regression.

Economic evaluation

The economic analysis consisted of a within-trial analysis of individual participant-level cost and effect (QALY) and a patient lifetime analysis to inform cost-effectiveness in the longer term. See *Chapter 5* for a detailed description of the methods used.

Qualitative research

Semistructured interviews were conducted with participants and clinicians and analysed according to the principles of thematic content analysis. See *Chapter 6* for a detailed description of the methods used.

Urodynamic quality assurance

A QA process was developed to ensure good-quality measurements and accurate urodynamics data recording. See *Chapter 7* for a detailed description of the methods used.

Management of the trial

The trial management team, based within CHaRT, provided day-to-day support for the recruiting sites led by a local PI. PIs, supported by dedicated research nurses, were responsible for all aspects of local organisation including recruitment of participants, delivery of the interventions and notification of any problems or unexpected developments during the trial period.

The trial was supervised by the project management group (PMG), which consisted of grant holders (clinicians, statisticians, health economists and qualitative researchers) and representatives from the Trial Office. The PMG met approximately every 2–3 months throughout the trial duration.

Oversight of the trial

Trial Steering Committee

A Trial Steering Committee (TSC) was established at the onset of the trial to oversee its conduct and progress. The TSC met seven times between October 2017 and February 2023 (approximately annually) and consisted of an independent chair, independent clinical and methodological experts, an independent patient representative and key members of the PMG. The independent members of the TSC are listed in the *Acknowledgements*.

Data-Monitoring Committee

An independent data monitoring committee (DMC) was established at the onset to oversee the safety of participants in the FUTURE trial. The committee met eight times between September 2017 and February 2023 at agreed intervals to monitor the trial data and make recommendations as to any required modifications to the protocol or the termination of all or part of the trial. It consisted of three independent experts, who are listed in the *Acknowledgements*.

Changes to the trial protocol

There were 10 protocol amendments during the lifetime of the project, most of which were minor clarifications. Amendments included a change to the randomisation algorithm from minimisation to stratified permuted blocks (prior to the first randomisation), an extension to the recruitment period due to a slower than expected recruitment rate and the COVID-19 pandemic, inclusion of an additional time point (24 months post randomisation) for those participants whose treatments have been delayed due to the pandemic, and conversion from written consent to verbal consent for the qualitative interviews. A summary of all changes can be found in the published protocol.[1]

All amendments were reviewed by the sponsor and funder before being submitted to and approved by the REC (where appropriate).

Chapter 3 Baseline results

This chapter describes how the participants were identified from 63 hospitals across the UK and reports the baseline characteristics up to the point of trial entry. The subsequent findings are described in *Chapter 4* (Clinical results), *Chapter 5* (Health Economic evaluation), *Chapter 6* (Qualitative study) and *Chapter 7* (Urodynamics quality assurance).

Between November 2017 and January 2021, 3066 potentially eligible women were screened, 1511 (49.3%) were confirmed eligible, of whom 1103 (73.0%) gave their consent and were randomised: 553 to receive urodynamics plus CCA and 550 to receive CCA only (*Figure 2*). There was a pause in recruitment between March 2020 and August 2020 due to the COVID-19 pandemic. The majority of participants were randomised prior to the pause, with only 81 participants (7.3%) randomised after August 2020: 43 to receive urodynamics plus CCA and 38 to receive CCA only.

Following randomisation, four participants were considered ineligible, recorded as post-randomisation exclusions and not included in any trial analyses (see *Figure 2*). This included one participant in the urodynamics plus CCA arm who was randomised after the recruitment pause. Therefore, 550 participants in the urodynamics plus CCA arm and 549 participants in the CCA only arm were included in the trial.

Study recruitment

The trial design and recruitment methodology have been reported previously[1] (see *Chapter 2*). Women with OAB or urgency-predominant MUI were identified at outpatient clinics or from urodynamic/outpatient waiting lists. Those meeting the eligibility criteria were invited to participate. The sites who participated in the FUTURE trial, including numbers recruited by site, are described in *Appendix 1* (see *Table 28*). The highest recruiting site was NHSG, with 92 randomised participants. This accounted for 8.3% of the total number randomised across the study, therefore no one site dominated recruitment. The recruitment rate is illustrated in *Figure 3*.

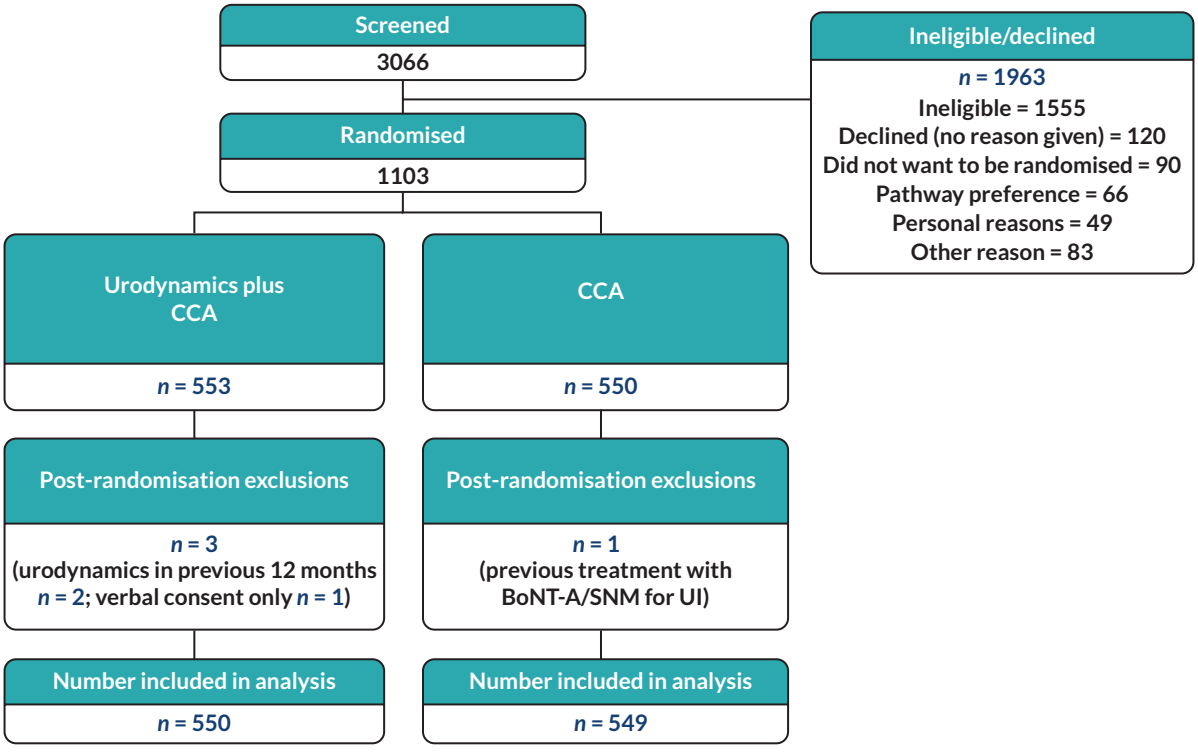

FIGURE 2 Flow of participants to the point of randomisation.

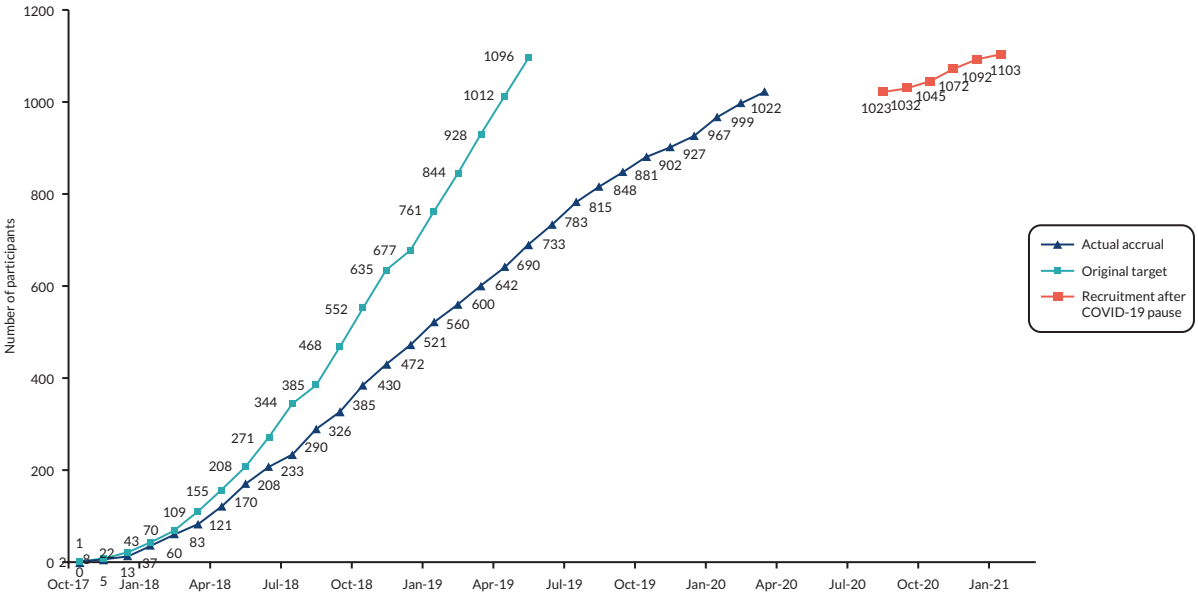

FIGURE 3 Recruitment to the trial over time.

Non-recruited participants

Of the 3066 participants approached, 1963 were either ineligible (*n* = 1555, 50.7%) or declined participation (*n* = 408; 13.3%; see *Appendix 1*, *Table 29*). Reasons for ineligibility included predominant SUI symptoms (*n* = 318; 20.5%), other clinical diagnosis not OAB or urgency-predominant MUI (*n* = 227; 14.6%), had not failed conservative management and/or two pharmacological treatments (*n* = 181; 11.6%), previous urodynamics in the last 12 months (*n* = 166; 10.7%), previous treatment with BoNT-A or SNM for UI (*n* = 140; 9.0%), neurogenic bladder (*n* = 93; 6.0%) and bladder pain syndrome (*n* = 78; 5.0%) (see *Appendix 1*, *Table 30*).

The most common reasons for participants declining to take part was an unwillingness to accept randomisation (*n* = 90; 22.1%), a preference for a particular clinical pathway (*n* = 66; 16.2%) and personal reasons (*n* = 49; 12.0%). One hundred and twenty participants (29.4%) did not provide a reason for declining trial participation (see *Appendix 1*, *Table 30*).

Randomised participants: baseline characteristics

The baseline characteristics for the 1099 participants who agreed to participate in the FUTURE trial and who were truly eligible to take part are described in *Tables 2* and *3*.

Participant characteristics

The two randomised groups were comparable at baseline (see *Table 2*). The mean age of participants was between 59 and 60 years. The BMI was similar in both groups at slightly > 30 kg/m^2. Almost 50% of women had BMI > 30. In both groups approximately two-thirds of the participants were diagnosed as predominantly OAB and one-third with urgency-predominant MUI.

Lab-confirmed UTIs and courses of antibiotics for UTIs were slightly more common in the women randomised to urodynamics plus CCA. Previous prolapse and SUI surgery rates were similar across both groups, with slightly < 30% of participants previously receiving surgery. PFMT was the most common previous conservative treatment. Current and previous OAB medical treatment use was similar between the two randomised groups.

TABLE 2 Baseline characteristics

	Urodynamics *N* = 550	CCA only *N* = 549
Age	59.3 (14.0); (*N* = 550)	59.8 (13.1); (*N* = 549)
BMI	30.6 (6.3); (*N* = 540)	30.9 (7.1); (*N* = 536)
BMI > 30	263 (47.8%)	257 (46.8%)
BMI > 35	120 (21.8%)	141 (25.7%)
Diagnosis		
OAB	363 (66.0%)	365 (66.5%)
MUI	187 (34.0%)	184 (33.5%)
Number of deliveries		
0	61 (11.1%)	63 (11.5%)
1	71 (12.9%)	86 (15.7%)
2	235 (42.7%)	204 (37.2%)
3 or more	174 (31.6%)	190 (34.6%)
Missing	9 (1.6%)	6 (1.1%)
Lab-confirmed UTI in last 12 months		
0	426 (77.5%)	402 (73.2%)
1	64 (11.6%)	69 (12.6%)
2	30 (5.5%)	40 (7.3%)
3 or more	30 (5.5%)	36 (6.6%)
Missing		2 (0.4%)
Courses of antibiotics for UTI in last 12 months		
0	386 (70.2%)	366 (66.7%)
1	60 (10.9%)	80 (14.6%)
2	45 (8.2%)	47 (8.6%)
3 or more	57 (10.4%)	53 (9.7%)
Missing	2 (0.4%)	3 (0.5%)
Received CISC training	15 (2.7%)	23 (4.2%)
Previous surgery		
SUI only	67 (12.2%)	74 (13.5%)
Prolapse only	72 (13.1%)	63 (11.5%)
Prolapse and SUI surgery	21 (3.8%)	25 (4.6%)
Current medication		
Anticholinergic drug	200 (36.4%)	202 (36.8%)
Betmiga	240 (43.6%)	226 (41.2%)
Low-dose prophylactic antibiotics	19 (3.5%)	22 (4.0%)
Previously tried betmiga	410 (74.5%)	388 (70.7%)

continued

TABLE 2 Baseline characteristics (*continued*)

	Urodynamics *N* = 550	CCA only *N* = 549
Previous conservative treatment		
Bladder training	377 (68.5%)	383 (69.8%)
PFMT	448 (81.5%)	474 (86.3%)
Percutaneous tibial nerve stimulation	28 (5.1%)	26 (4.7%)
Acupuncture	17 (3.1%)	15 (2.7%)
Biofeedback	26 (4.7%)	19 (3.5%)
Baseline bladder diary summary	406 (73.8%)	372 (67.8%)
Daytime frequency	7.9 (3.8); (*N* = 396)	7.9 (3.2); (*N* = 367)
Daytime frequency > 7 per day	208/396 (52.5%)	180/367 (49.0%)
Nocturia	1.9 (1.5); (*N* = 394)	2.0 (1.4); (*N* = 366)
Nocturnal frequency > 2 per day	133/394 (33.8%)	141/366 (38.5%)
Number mild urgency episodes per 24 hours	1.3 (1.8); (*N* = 351)	1.0 (1.4); (*N* = 331)
Number moderate urgency episodes per 24 hours	3.3 (3.1); (*N* = 351)	3.1 (2.8); (*N* = 331)
Number severe urgency episodes per 24 hours	2.8 (2.8); (*N* = 353)	3.1 (3.4); (*N* = 333)
UI episodes per 24 hours	4.3 (3.7); (*N* = 405)	4.4 (3.9); (*N* = 370)
UUI episodes per 24 hours	2.9 (3.3); (*N* = 405)	3.0 (3.2); (*N* = 370)
SUI episodes per 24 hours	0.2 (0.6); (*N* = 405)	0.2 (0.7); (*N* = 370)

Note
Reproduced from Abdel-Fattah *et al*. Invasive urodynamic investigations in the management of women with refractory overactive bladder symptoms (FUTURE) in the UK: a multicentre, superiority, parallel, open-label, randomised controlled trial. *Lancet* 2025;**405**:1057–68. https://doi.org/10.1016/S0140-6736(2401886-5. This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The table includes minor additions and formatting changes to the original text.

Health-related quality of life scores at baseline

The baseline questionnaire scores show the two groups as similar (see *Table 3*). The mean EQ-5D-5L is 0.02 higher for those randomised to CCA only (the higher scores indicate better HRQoL). However, as the baseline scores in both groups range from very poor HRQoL to excellent HRQoL, there is a large amount of uncertainty, and this difference is relatively small. In comparison, the mean EQ-5D-5L score for females in the age range 60–64 is 0.776 (0.769, 0.797) and the FUTURE trial population is therefore more than 0.1 lower.[74]

The mean ICIQ-LUTS HRQoL scores are close to the midpoint of the range in both randomised groups and, overall, scores are seen on close to the full range of the scale (see *Table 3*).

On the ICIQ-FLUTS filling score, ICIQ-FLUTS incontinence score and ICIQ-OAB score, some women were reporting the maximum impact. The everyday-life interference also shows women's symptoms as having a major impact on their lives (see *Table 3*). Over 90% of participants perceive their urgency as either moderate or severe on the UPS (see *Table 3*).

Baseline 3-day bladder diary

The baseline bladder diaries were completed by 778 participants [406 participants (73.8%) in the urodynamic arm and 372 participants in the CCA arm (67.8%)]. Daytime frequency and nocturia were very similar in both groups at a mean of 7.9 [standard deviation (SD) 3.8] compared to 7.9 (SD 3.2) and a mean of 1.9 (SD 1.5) compared to 2.0 (SD 1.4)

TABLE 3 Baseline quality-of-life measures

	Urodynamics *N* = 550	**CCA only** *N* = 549
How much do urinary symptoms interfere with your everyday life?	8.0 (2.1); (*N* = 530)	7.9 (2.0); (*N* = 533)
ICIQ-FLUTS filling score	8.4 (2.7); (*N* = 527)	8.4 (2.8); (*N* = 530)
ICIQ-FLUTS voiding score	2.6 (2.6); (*N* = 530)	2.5 (2.3); (*N* = 536)
ICIQ-FLUTS incontinence score	10.5 (4.6); (*N* = 528)	10.8 (4.3); (*N* = 527)
ICIQ-OAB score	10.0 (2.7); (*N* = 531)	10.2 (2.7); (*N* = 533)
ICIQ-LUTS HRQoL score	51.8 (12.1); (*N* = 497)	52.3 (12.8); (*N* = 497)
EQ-5D-5L	0.653 (0.290); (*N* = 531)	0.674 (0.293); (*N* = 529)
UPS		
None	2 (0.4%)	5 (0.9%)
Mild	10 (1.8%)	12 (2.2%)
Moderate	156 (28.4%)	151 (27.5%)
Severe	353 (64.2%)	345 (62.8%)
Missing	29 (5.3%)	36 (6.6%)

Notes
1. The summary in each cell is mean (standard deviation); *N*.
2. How much do urinary symptoms interfere is on the scale 0–10, with a higher score indicating more interference.
3. The filling score is on the scale 016, with a higher score indicating greater symptom severity.
4. The voiding score is on the scale 0–12, with a higher score indicating greater symptom severity.
5. The incontinence score is on the scale 0–20, with a higher score indicating greater symptom severity.
6. The OAB score is on the scale 0–16, with a higher score indicating greater symptom severity.
7. The LUTS-QoL score is on the scale 19–76, with higher scores indicating lower HRQoL.
8. The EQ-5D-5L responses are transformed onto a scale from −0.594 to 1, with higher scores indicating better HRQoL.

respectively. Of the CCA only participants 38.5% had nocturia > 2 voiding episodes per day compared to 33.8% of the urodynamics plus CCA participants, while a higher percentage of urodynamics participants (52.5% compared to 49.0%) had a daytime frequency > 7 voiding episodes per day.

Urgency was slightly higher in the CCA only group, with participants reporting a mean of 1.0 (SD 1.4) mild episodes and 3.1 (SD 3.4) severe episodes, compared to 1.3 (SD 1.8) and 2.8 (SD 2.8) respectively in the urodynamics group plus CCA. There were no differences in the number of UI episodes between participants in both groups.

Chapter 4 Clinical results

This chapter compares the clinical outcomes of urodynamics plus CCA versus CCA only at 3 months, 6 months and the final follow-up time point, which was either 15 or 24 months post randomisation, as detailed in *Chapter 2*.

Flow of participants through the trial

The CONsolidated Standards of Reporting Trials (CONSORT) diagram shows the number of participants providing data at each stage of the trial (*Figure 4*). There were 1103 participants randomised into the trial. Following randomisation, four participants were considered post-randomisation exclusions: three from the group randomised to urodynamics plus CCA (referred to as the urodynamics arm) and one from the group randomised to CCA only (referred to as the CCA only arm). This chapter reports the results from the remaining 1099 women.

Response rates to questionnaires are based on the numbers of participants randomised after accounting for post-randomisation exclusions. Completion rates of the participant questionnaires from 6 months onwards are above 90% (response rates are reported in the CONSORT diagram; see *Figure 4*). Participant-reported primary outcome data could not be collected from 53 participants who declined further follow-up (n = 48) or died (n = 5) during the follow-up period.

Intervention details

Of the 1099 participants included in the analysis, 491/550 (89.3%) randomised to urodynamics and 522/549 (95.1%) randomised to CCA only received the allocated assessment (intervention). Of those randomised to CCA only, 8 participants (1.5%) underwent urodynamics, whereas 13 participants randomised to urodynamics (2.4%) received CCA only. The remaining 65 participants (46 in the urodynamics arm and 19 in the CCA only arm) did not receive either intervention.

In both arms, participants underwent a detailed clinical assessment as per NICE guidelines[3] and standard clinical practice in each of the collaborating sites. This included a detailed history-taking, abdominal and pelvic examination and a 3-day bladder diary.

In their clinical assessment, many clinicians/hospitals adopted the FUTURE trial purposely designed bladder diaries, while some used their standard bladder diaries to avoid duplication and reduce participant burden. The results of the bladder diaries in both arms are presented later in the chapter.

Urodynamics

Uroflowmetry

Table 4 shows that the uroflowmetry performed as part of the urodynamics assessment (392 participants in the urodynamics arm and 5 participants in the CCA only arm) was mostly conducted by either a nurse (229/397; 57.7%) or a hospital specialist (154/397; 38.8%). The operator's impression of the uroflowmetry voiding pattern for two-thirds of the procedures was normal (275/397; 69.3%).

The median voided volume was 121 ml for those randomised to urodynamics [interquartile range (IQR) 57–233 ml] and 101 ml (IQR 51–225 ml) for those randomised to CCA only, and the PVR were 10 ml (IQR 0–40 ml) and 2 ml (IQR 0.5–16.5 ml) respectively. PVR urine volume was > 100 ml in 12.3% of participants undergoing uroflowmetry as part of the urodynamics assessment (compared to 12.6% of women in the CCA only arm with PVR > 100 ml on bladder scan).

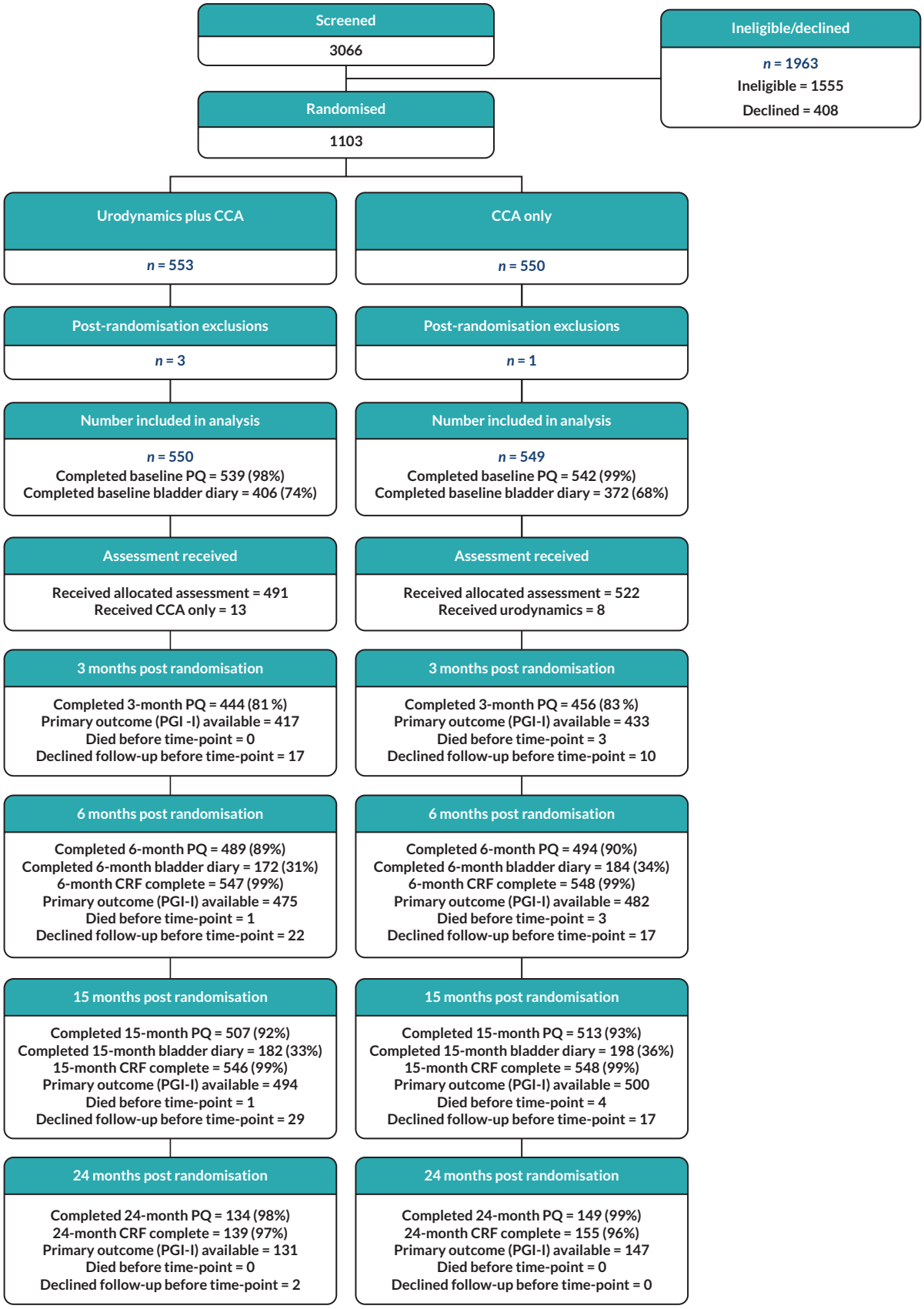

FIGURE 4 Consolidated Standards of Reporting Trials diagram.

TABLE 4 Summary of urodynamic and CCA data

	Urodynamics *N* = 550	CCA only *N* = 549
Urodynamic assessment		
Uroflowmetry		
Uroflowmetry performed	392 (71.3%)	5 (0.9%)
Health professional performing intervention		
Nurse	226 (57.7%)	3 (60.0%)
Hospital specialist	153 (39.0%)	1 (20.0%)
Doctor in training	6 (1.5%)	
Missing	7 (1.8%)	1 (20.0%)
Voided volumes		
Voided volume (ml)	121.0; (57.0, 233.0); (*N* = 377)	101.0; (51.0, 225.0); (*N* = 5)
Post-voiding residual (ml)	10.0; (0.0, 40.0); (*N* = 367)	2.0; (0.5, 16.5); (*N* = 4)
Post-voiding residual > 100 ml	45 (12.3%)	0 (0.0%)
Operators impression of voiding pattern		
Normal	271 (69.1%)	4 (80.0%)
Voiding dysfunction	55 (14.0%)	
Missing	66 (16.8%)	1 (20.0%)
Cystometry		
Cystometry performed	489 (88.9%)	7 (1.3%)
Healthcare professional performing cystometry		
Nurse	299 (61.1%)	5 (71.4%)
Staff doctor or specialist	197 (40.3%)	2 (28.6%)
Doctor in training	19 (3.9%)	
Technologist	24 (4.9%)	
Filling cystometry		
Filling rate < 50 ml/minute	68/489 (13.9%)	1/7 (14.3%)
Filling rate ≥ 50 and < 100 ml/minute	306/489 (62.6%)	3/7 (42.9%)
Filling rate ≥ 100 ml/minute	100/489 (20.4%)	
First sensation of filling (ml)	93.0; (49.5, 150.0); (*N* = 388)	77.0; (38.0, 141.0); (*N* = 5)
First desire to void (ml)	118.0; (71.0, 185.0); (*N* = 435)	81.0; (56.0, 141.0); (*N* = 6)
Normal desire to void (ml)	167.0; (104.0, 248.0); (*N* = 398)	270.0; (141.0, 311.0); (*N* = 5)
Strong desire to void (ml)	232.7; (155.0, 339.0); (*N* = 434)	141.0; (123.0, 363.0); (*N* = 5)
Maximum cystometric capacity (ml)	347.0; (253.0, 432.6); (*N* = 469)	300.0; (143.0, 400.0); (*N* = 7)
Voiding cystometry		
Voided volume (ml)	314.0; (199.0, 445.0); (*N* = 471)	194.5; (101.0, 319.0); (*N* = 6)
Maximum flow rate (ml/second)	16.3; (10.1, 24.0); (*N* = 448)	16.0; (13.6, 20.6); (*N* = 6)
Average flow rate (ml/second)	6.7; (3.3, 10.8); (*N* = 388)	3.8; (1.9, 7.0); (*N* = 5)

TABLE 4 Summary of urodynamic and CCA data (*continued*)

	Urodynamics *N* = 550	CCA only *N* = 549
Detrusor pressure at max flow (cmH_2O)	29.0; (18.0, 40.0); (*N* = 406)	21.0; (15.0, 43.0); (*N* = 5)
Residual urine (ml)	0.0; (0.0, 45.0); (*N* = 448)	0.0; (0.0, 34.0); (*N* = 5)
Operators impression of voiding pattern		
Normal	347 (71.0%)	6 (85.7%)
Detrusor underactivity	40 (8.2%)	
Acontractile detrusor	8 (1.6%)	
Bladder outflow obstruction	29 (5.9%)	
Intermittent	17 (3.5%)	
Fluctuating	9 (1.8%)	
Missing	45 (9.2%)	1 (14.3%)
Intrinsic sphincter deficiency tests		
Tests performed	49 (8.9%)	
Maximum urethral closure pressure (cmH_2O)	64.0; (48.0, 82.1); (*N* = 51)	
Diagnosis following urodynamics		
Diagnosis available	487 (88.5%)	7 (1.3%)
DO/DOI	281 (57.7%)	6 (85.7%)
USI	65 (13.3%)	
MUI	39 (8.0%)	
No evidence of any of the above conditions	102 (20.9%)	1 (14.3%)
CCA only		
Uroflowmetry		
Uroflowmetry performed	3 (0.5%)	257 (46.8%)
Health professional performing intervention		
Nurse	2 (66.7%)	173 (67.3%)
Hospital specialist	1 (33.3%)	77 (30.0%)
Doctor in training		7 (2.7%)
Voided volumes		
Voided volume (ml)	170.0; (162.0, 188.0); (*N* = 3)	176.0; (103.0, 282.0); (*N* = 253)
Post-voiding residual (ml)	0.0; (0.0, 20.0); (*N* = 3)	20.0; (0.0, 55.0); (*N* = 240)
Post-voiding residual > 100 ml	0 (0.0%)	37 (15.4%)
Maximum flow rate (ml/second)	15.4; (11.2, 28.0); (*N* = 3)	16.1; (10.7, 26.0); (*N* = 234)
Average flow rate (ml/second)	6.2; (0.0, 12.4); (*N* = 2)	7.7; (4.8, 11.0); (*N* = 205)
Operators impression of voiding pattern		
Normal	3 (100.0%)	195 (75.9%)
Voiding dysfunction		37 (14.4%)

continued

TABLE 4 Summary of urodynamic and CCA data (*continued*)

	Urodynamics *N* = 550	CCA only *N* = 549
Missing		25 (9.7%)
Bladder scan		
Bladder scan performed	3 (0.5%)	349 (63.6%)
Voided volumes		
Voided volume (ml)	188.0; (188.0, 188.0); (*N* = 1)	150.0; (75.0, 220.0); (*N* = 191)
Post-voiding residual (ml)	0.0; (0.0, 0.0); (*N* = 1)	10.0; (0.0, 49.0); (*N* = 231)
Post-voiding residual > 100 ml	0 (0.0%)	29 (12.6%)
Diagnosis following CCA only		
Diagnosis available	1 (0.2%)	354 (64.5%)
OAB/UUI	1 (100.0%)	222 (62.7%)
SUI		4 (1.1%)
Urgency-predominant MUI		118 (33.3%)
Other		10 (2.8%)

Filling and voiding cystometry

For the participants who received cystometry as part of the urodynamic assessment (489 participants in the urodynamics arm and 7 participants in the CCA only arm), the procedure was mainly performed by a nurse (304/496; 61.3%) or staff doctor/specialist (199/496; 40.1%).

Of those randomised to urodynamics, 68 (13.9%) had a filling rate < 50 ml/minute, 306 (62.6%) had a filling rate ≥ 50 and < 100 ml/minute, and 100 (20.4%) had a filling rate of 100 ml/minute or above.

Participants in the urodynamics arm reported their first desire to void at a median of 118 ml (IQR 71–185 ml) and a strong desire to void at a median of 232.7 ml (IQR 155–339 ml). In terms of the maximum cytometric capacity, the median volumes were 347 ml (IQR 253–432.6). The operator's impression of the voiding pattern was normal in 71% of the cases (347/489).

Following urodynamics, 57.7% of the women were diagnosed with DO or detrusor overactivity incontinence (DOI) and 8.0% were diagnosed with urodynamic MUI. Thirteen per cent had USI, while 21% had neither DO/DOI nor USI on urodynamics. Hence, in women with clinical refractory OAB/MUI, urodynamics did not show evidence of DO in 34% of women.

When adjusted for the baseline clinical diagnosis:

- In the group of participants with a baseline diagnosis of OAB, their diagnosis following urodynamics was DO/DOI in 62.3% of cases, MUI in 6.2%, no evidence of USI or DO in 21.9% and USI in 8.3% of cases. Hence, in women with clinical refractory OAB, urodynamics did not show evidence of DO in 30% of women.
- In the group of participants with a baseline diagnosis of urgency-predominant MUI, their diagnosis following urodynamics was DO/DOI in 48.6% of cases, MUI in 10.9%, no evidence of USI or DO in 18.3% and USI in 21.7% of cases. Hence, in women with clinical refractory MUI, urodynamics did not show evidence of DO in 40% of women.

It is notable that USI was diagnosed following urodynamics in 8.3% and 21.7% of women with a baseline diagnosis of OAB and urgency-predominant MUI respectively. This diagnosis would lead to a change in their management plan according to the national and international clinical guidelines and the FUTURE trial treatment pathways.

Comprehensive clinical assessment

Uroflowmetry

For the participants who received uroflowmetry as part of the CCA (3 participants in the urodynamics arm and 257 participants in the CCA only arm), the procedure was primarily conducted by either a nurse (175/260; 67.3%) or a hospital specialist (78/260; 30.0%) and the operator's impression of the voiding pattern was normal in approximately three-quarters of the cases (198/260; 76.2%) (see *Table 4*).

The median voided volume was 176 ml for those randomised to CCA only (IQR 103–282 ml) and 170 ml (IQR 162–188 ml) for those randomised to urodynamics, and the PVRs were 20 ml (IQR 0–55 ml) and 0 ml (IQR 0–20 ml), respectively. PVR urine volume was > 100 ml in 15.4% of participants in the CCA only arm.

Bladder scan

Three hundred and fifty-two women (3 women in the urodynamics arm and 349 women in the CCA only arm) underwent a bladder scan as part of their intervention. The median voided volume was 150 ml for those randomised to CCA only (IQR 75–220 ml) and 188 ml for the women randomised to urodynamics, and the PVRs were 10 ml (IQR 0–49 ml) and 0 ml, respectively. PVR urine volume was > 100 ml in 12.6% of those undergoing a bladder scan (see *Table 4*).

Following CCA, 63% were diagnosed with OAB/UUI; 33% had urgency-predominant MUI; 1% SUI and 3% other diagnoses.

Primary outcome: participant-reported success rates

The primary outcome was the proportion of participants who reported success at their final follow-up time point (15 or 24 months post randomisation). Success was a participant response of either 'very much improved' or 'much improved' to the question 'How would you describe your urinary/bladder problems (urgency and/or incontinence) now compared to when you joined the study?' on the PGI-I assessment tool [i.e. comparing their symptoms in the last 2 weeks (at time of completing the questionnaire) to their symptoms on the day they were randomised]. All other responses to this question ('improved', 'same', 'worse', 'much worse' and 'very much worse') were considered as unsuccessful.

At the final follow-up time point, 117 participants (23.6%) in the urodynamics arm and 114 participants (22.7%) in the CCA only arm reported success as 'very much improved' or 'much improved' (*Table 5*). The adjusted OR was 1.12 (95% CI 0.73 to 1.74; $p = 0.601$); that is, no significant difference between the groups. The per protocol success rates [113 (24.9%) vs. 111 (23.0%)] and effect sizes [1.22 (95% CI 0.78 to 1.91); $p = 0.390$] were similar to the ITT estimates. These results confirm that in women with refractory OAB/urgency-predominant MUI, the participant-reported success rates following treatment in participants who underwent urodynamics and CCA were not superior to those who underwent CCA only.

The success rates and effect sizes at 3 and 6 months favour CCA only, but this can be explained by the additional investigation delaying treatment for those randomised to urodynamics.

Sensitivity analysis

Figure 5 shows the sensitivity analysis of the participant-reported success on the PGI-I for the ITT population. The forest plot shows the observed effect as being consistent with the effect sizes obtained under multiple imputation and when all missing primary outcome data are assumed to be unsuccessful and then when all missing primary outcome data are assumed to be success. The only instances where the observed effect is not consistent with the imputation

TABLE 5 Primary outcome (PGI-I) ITT and per protocol at 3 and 6 months and the last follow-up

	Urodynamics *N* = 550	CCA only *N* = 549	OR (95% CI); *p*-value
Questionnaire response rates			
3-month questionnaire	444/550 (80.7%)	456/549 (83.1%)	
6-month questionnaire	489/550 (88.9%)	494/549 (90.0%)	
Questionnaire at last follow-up[a]	507/550 (92.2%)	513/549 (93.4%)	
PGI-I success[b]			
3 months	34/417 (8.2%)	77/433 (17.8%)	0.28 (0.16 to 0.51); < 0.001
6 months	99/475 (20.8%)	122/482 (25.3%)	0.68 (0.43 to 1.06); 0.090
Last follow-up	117/496 (23.6%)	114/503 (22.7%)	1.12 (0.73 to 1.74); 0.601
PGI-I success (less strict)[c]			
3 months	75/417 (18.0%)	114/433 (26.3%)	0.49 (0.31 to 0.77); 0.002
6 months	166/475 (34.9%)	203/482 (42.1%)	0.64 (0.44 to 0.93); 0.020
Last follow-up	217/496 (43.8%)	209/503 (41.6%)	1.14 (0.79 to 1.65); 0.469
Questionnaire response rates (per protocol analysis)			
3-month questionnaire	407/550 (74.0%)	438/549 (79.8%)	
6-month questionnaire	449/550 (81.6%)	476/549 (86.7%)	
Questionnaire at last follow-up[a]	464/550 (84.4%)	493/549 (89.8%)	
PGI-I success (per protocol)[b]			
3 months	30/382 (7.9%)	74/416 (17.8%)	0.26 (0.14 to 0.49); < 0.001
6 months	94/437 (21.5%)	120/464 (25.9%)	0.68 (0.43 to 1.08); 0.104
Last follow-up	113/454 (24.9%)	111/483 (23.0%)	1.22 (0.78 to 1.91); 0.390
PGI-I success (less strict per protocol)[c]			
3 months	68/382 (17.8%)	111/416 (26.7%)	0.48 (0.30 to 0.76); 0.002
6 months	156/437 (35.7%)	198/464 (42.7%)	0.65 (0.44 to 0.96); 0.032
Last follow-up	205/454 (45.2%)	204/483 (42.2%)	1.21 (0.83 to 1.76); 0.325
How would you describe your urinary/bladder problems over the last 2-weeks?			
3-month time point			
Very much improved	19/417 (4.6%)	48/433 (11.1%)	
Much improved	15/417 (3.6%)	29/433 (6.7%)	
Improved	41/417 (9.8%)	37/433 (8.5%)	
No change	219/417 (52.5%)	203/433 (46.9%)	
Worse	70/417 (16.8%)	66/433 (15.2%)	
Much worse	36/417 (8.6%)	34/433 (7.9%)	
Very much worse	17/417 (4.1%)	16/433 (3.7%)	

TABLE 5 Primary outcome (PGI-I) ITT and per protocol at 3 and 6 months and the last follow-up (*continued*)

	Urodynamics *N* = 550	CCA only *N* = 549	OR (95% CI); *p*-value
6-month time point			
Very much improved	65/475 (13.7%)	76/482 (15.8%)	0.82 (0.66 to 1.02); 0.081
Much improved	34/475 (7.2%)	46/482 (9.5%)	
Improved	67/475 (14.1%)	81/482 (16.8%)	
No change	182/475 (38.3%)	159/482 (33.0%)	
Worse	81/475 (17.1%)	68/482 (14.1%)	
Much worse	24/475 (5.1%)	25/482 (5.2%)	
Very much worse	22/475 (4.6%)	27/482 (5.6%)	
Last follow-up time point			
Very much improved	64/496 (12.9%)	59/503 (11.7%)	1.07 (0.88 to 1.30); 0.480
Much improved	53/496 (10.7%)	55/503 (10.9%)	
Improved	100/496 (20.2%)	95/503 (18.9%)	
No change	156/496 (31.5%)	163/503 (32.4%)	
Worse	61/496 (12.3%)	64/503 (12.7%)	
Much worse	33/496 (6.7%)	45/503 (8.9%)	
Very much worse	29/496 (5.8%)	22/503 (4.4%)	

a For participants who received and responded to the 24-month questionnaire this was their final follow-up. If a participant was not eligible for the 24-month follow-up (or received it but did not respond) then the 15-month questionnaire was their final follow-up.
b Success was a participant response of either 'very much improved' or 'much improved' to the PGI-I question 'How would you describe your urinary/bladder problems (urgency and/or incontinence) now compared to when you joined the study?'. All other responses to the question were considered unsuccessful.
c A less strict definition where 'improved' was also included in the definition of success.

Notes
Last follow-up:
1. The summary in each cell is count and percentage.
2. The effect size comes from a mixed-effects logistic regression. Random effects (intercept) are included for site and participant. Fixed effects are included for the treatment variable, presence of a 24-month follow-up, time from randomisation to follow-up and baseline diagnosis of OAB. Dummy variables are also included for time point and an interaction of these, and the treatment variables are included to allow the treatment effect to be estimated at each time point.
3. The effect size for the full PGI-I is obtained using a partial proportional odds model at each time point. Robust variances are used to adjust for clustering by site. Fixed effects are included for the treatment variable, diagnosis of OAB at baseline, presence of a 24-month follow-up and time from randomisation to follow-up. As the assumption of parallel lines does not hold at 3 months there is not a single effect size to present. The parallel lines assumption does hold at 6 months and the final follow-up point so it is possible to present a single effect size.

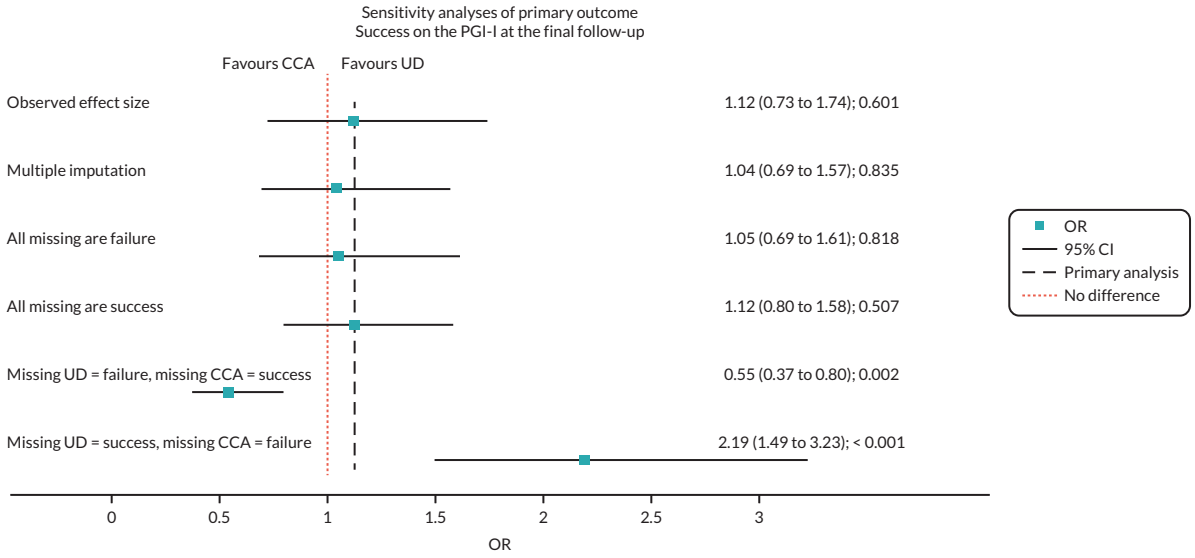

FIGURE 5 Sensitivity analysis forest plot (ITT population).

effects are in the extreme cases when all missing primary outcome data are assumed to be a success for those undergoing urodynamics but unsuccessful for those undergoing CCA only and vice versa.

Secondary outcomes

Less strict definition of participant-reported success

A 'less strict definition of success' which included participant response of 'improved', 'much improved' and 'very much improved' was analysed as a secondary outcome. Inclusion of 'improved' had the effect of increasing the number of women reporting success in both the urodynamic arm [217 women (43.8%)] and the CCA only arm [209 women (41.6%)]. However, the effect size at the last follow-up time point was similar, at 1.14 (95% CI 0.79 to 1.65); $p = 0.469$ (see *Table 5*). This further confirms the robustness of results of the primary outcome.

Participant-reported success for those receiving botulinum toxin injection A

The most commonly utilised treatment in the FUTURE trial was BoNT-A, with 620 women receiving this treatment.

Restricting the PGI-I assessment to only those women receiving BoNT-A, the participant-reported success rate using the primary definition of success ('very much improved' and 'much improved') at the 3-month time point favoured the CCA only arm. However, at the final follow-up questionnaire time point, there were no significant differences: 36.7% versus 31.0% [OR: 1.40 (95% CI 0.87 to 2.23); $p = 0.164$] in the urodynamics arm and the CCA only arm, respectively (*Table 6*). Using the less strict definition of success (inclusion of 'improved'), once again significantly more women in the CCA only arm reported a successful outcome at 3-month follow-up. However, at the final time point, the participant-reported success rate favoured the urodynamics arm: 61.4% versus 51.8% [OR 1.63 (95% CI 1.09 to 2.45); $p = 0.018$] in the urodynamics arm and the CCA only arm, respectively (see *Table 6*).

In participants receiving BoNT-A treatment, the fixed time points for assessment may have had an impact on the study results primarily due to the temporal effect of BoNT-A, where treatment tends to start waning 4 to 6 months post treatment. Hence, these fixed assessment time points may miss the peak effect of BoNT-A treatment. Therefore, in the final follow-up questionnaire, the group of women who received BoNT-A were asked an extra question to describe their PGI-I outcome '2 months following treatment'. The women's responses to this question can therefore be the best representative of the participant-reported success rates for the subgroup who received BoNT-A treatment.

Using the primary definition of success on the PGI-I ('very much improved' and 'much improved'), the participant-reported success rate was 63.8% versus 60.0% [OR: 1.17 (95% CI 0.73 to 1.89); $p = 0.518$] in the urodynamics arm

TABLE 6 Summary of PGI-I success for women receiving BoNT-A

	Urodynamics *N* = 266	CCA only *N* = 336	OR OR (99% CI); *p*-value
Questionnaire response rates			
3-month questionnaire	239/277 (86.3%)	296/343 (86.3%)	
6-month questionnaire	264/277 (95.3%)	323/343 (94.2%)	
Last follow-up	270/277 (97.5%)	331/343 (96.5%)	
PGI-I success[a]			
3 months	27/220 (12.3%)	64/280 (22.9%)	0.35 (0.19 to 0.66); 0.001
6 months	86/257 (33.5%)	107/317 (33.8%)	0.93 (0.58 to 1.50); 0.768
Last follow-up	98/267 (36.7%)	101/326 (31.0%)	1.40 (0.87 to 2.23); 0.164
PGI-I success (less strict)[b]			
3 months	44/220 (20.0%)	86/280 (30.7%)	0.47 (0.28 to 0.77); 0.003
6 months	120/257 (46.7%)	161/317 (50.8%)	0.78 (0.52 to 1.18); 0.243
Last follow-up	163/267 (61.4%)	169/326 (51.8%)	1.63 (1.09 to 2.45); 0.018
PGI-I success 2 months after BoNT-A[c]			
Original definition	88/138 (63.8%)	99/165 (60.0%)	1.17 (0.73 to 1.89); 0.518
Less strict definition	115/138 (83.3%)	126/165 (76.4%)	1.47 (0.82 to 2.63); 0.195

a Success was a participant response of either 'very much improved' or 'much improved' to the PGI-I question 'How would you describe your urinary/bladder problems (urgency and/or incontinence) now compared to when you joined the study?'. All other responses to the question were considered unsuccessful.
b A less strict definition where 'improved' was also included in the definition of success.
c PGI-I success 2 months after BoNT-A was the response to a question asked in the final follow-up for women who received BoNT-A. These women were asked to describe their urinary/bladder problems in the first 2 months following their BoNT-A injection on the PGI-I scale. Response rates are lower as this additional question was not asked during the final reminder phone-call.

Notes
1. The summary in each cell is count and percentage.
2. The effect size comes from a mixed-effects logistic regression. Random effects (intercept) are included for site and participant. Fixed effects are included for the treatment variable, presence of a 24-month follow-up, time from randomisation to follow-up and baseline diagnosis of OAB. Dummy variables are also included for time point and an interaction of these, and the treatment variables are included to allow the treatment effect to be estimated at each timepoint.
3. The effect size for the full PGI-I is obtained using a partial proportional odds model at each time point. Robust variances are used to adjust for clustering by site. Fixed effects are included for the treatment variable, diagnosis of OAB at baseline, presence of a 24-month follow-up and time from randomisation to follow-up. As the assumption of parallel lines does not hold at 3 months there is not a single effect size to present. The parallel lines assumption does hold at 6 months and the final follow-up point so it is possible to present a single effect size.

and the CCA only arm, respectively (see *Table 6*). Using the less strict definition of success (inclusion of 'improved') the participant-reported success rate was 83.3% versus 76.4% [OR: 1.47 (95% CI 0.82 to 2.63); $p = 0.195$] in the urodynamics arm and the CCA only arm, respectively (see *Table 6*). The results indicate no evidence of significant differences in participant-reported success rates following BoNT-A treatment between the two groups. These results provide further reassurance in the primary outcome analyses.

Pre-planned subgroup analyses of the primary outcome

The participant-reported success rates within the subgroups (baseline clinical diagnosis of OAB vs. urgency-predominant MUI) are shown at 3 and 6 months and the final follow-up time point in *Table 7*. At 3-month follow-up, women in the CCA only arm had significantly higher participant-reported success rates in both subgroups (see *Table 7*). However, at the final time point the difference in both subgroups was not significant. This is best explained by the time to receiving treatment, which is shorter in the CCA arm as they did not have to wait to undergo urodynamics. The mean

TABLE 7 Subgroup analysis by baseline clinical diagnosis (ITT population)

	Urodynamics *N* = 550	CCA only *N* = 549	OR OR (99% CI); *p*-value
3 months			
PGI-I success			
OAB	29/276 (10.5%)	51/293 (17.4%)	0.42 (0.17 to 1.03); 0.013
MUI	5/141 (3.5%)	26/140 (18.6%)	0.09 (0.02 to 0.45); < 0.001
PGI-I success (less strict)			
OAB	56/276 (20.3%)	76/293 (25.9%)	0.61 (0.30 to 1.24); 0.072
MUI	19/141 (13.5%)	38/140 (27.1%)	0.31 (0.10 to 0.90); 0.005
6 months			
PGI-I success			
OAB	70/311 (22.5%)	87/323 (26.9%)	0.67 (0.33 to 1.38); 0.154
MUI	29/164 (17.7%)	35/159 (22.0%)	0.69 (0.24 to 1.99); 0.365
PGI-I success (less strict)			
OAB	115/311 (37.0%)	136/323 (42.1%)	0.71 (0.39 to 1.31); 0.153
MUI	51/164 (31.1%)	67/159 (42.1%)	0.51 (0.22 to 1.21); 0.044
Final follow-up			
PGI-I success			
OAB	81/326 (24.8%)	78/333 (23.4%)	1.17 (0.58 to 2.36); 0.560
MUI	36/170 (21.2%)	36/170 (21.2%)	1.03 (0.37 to 2.84); 0.940
PGI-I success (less strict)			
OAB	143/326 (43.9%)	138/333 (41.4%)	1.17 (0.65 to 2.11); 0.494
MUI	74/170 (43.5%)	71/170 (41.8%)	1.09 (0.48 to 2.48); 0.782
PGI-I success 2 months after BoNT-A[a]			
OAB	61/98 (62.2%)	66/109 (60.6%)	1.07 (0.50 to 2.28); 0.816
MUI	27/40 (67.5%)	33/56 (58.9%)	1.44 (0.45 to 4.56); 0.416

a PGI-I success 2 months after BoNT-A was the response to a question asked in the final follow-up for women who received BoNT-A. These women were asked to describe their urinary/bladder problems in the first 2 months following their BoNT-A injection on the PGI-I scale.

Notes
1. The summary in each cell is count and percentage.
2. The effect size comes from a mixed-effects logistic regression. Random effects (intercept) are included for site and participant. Fixed effects are included for the treatment variable, presence of a 24-month follow-up, time from randomisation to follow-up and baseline diagnosis of OAB. Dummy variables are also included for time point and an interaction of these, and the treatment variables are included to allow the treatment effect to be estimated at each time point. Interaction of the treatment variable and baseline diagnosis, baseline diagnosis and time point and three-way interaction of treatment, diagnosis and time point are also included to allow the subgroup effects to be estimated.

time to receiving the first dose of BoNT-A was 234.3 days in the urodynamics arm compared to 188.4 days in the CCA arm; that is, women in the CCA only arm have the opportunity to start to feel improvement in their symptoms earlier.

The urodynamic effects plotted in *Figure 6* further show the subgroup effects at the final follow-up time point. The ORs of 1.14 (99% CI 0.33 to 3.90; $p = 0.788$) and 1.07 (99% CI 0.39 to 2.95; $p = 0.861$) for the original and less

strict definitions of success, respectively, show that there is no evidence of a significant difference in the impact of urodynamics between participants with baseline clinical diagnosis of OAB compared to urgency-predominant MUI.

Undertaking the same subgroup analysis in participants who received BoNT-A treatment, the participant-reported success rates were not significantly different between the groups. In participants with a clinical diagnosis of OAB at baseline, the participant-reported success rates were 61/98 (62.2%) in the urodynamics arm versus 66/109 (60.6%) in the CCA only arm [OR 1.07 (99% CI 0.50 to 2.28); p = 0.816], while in participants with a baseline diagnosis of urgency-predominant MUI, the participant-reported success rates were 27/40 (67.5%) in the urodynamics arm and 33/56 (58.9%) in the CCA only arm [OR 1.44 (99% CI 0.45 to 4.56); p = 0.416].

The difference between the OAB and urgency-predominant MUI groups was non-significant [OR 0.74 (99% CI 0.19 to 2.96); p = 0.581], indicating that among participants who underwent BoNT-A treatment, urodynamics appears to be more effective in the urgency-predominant MUI group compared to OAB. However, the difference was not significant.

Urinary symptoms

The International Consultation on Incontinence Questionnaire female lower urinary tract symptoms

The ICIQ-FLUTS scores in the filling, voiding and incontinence domains improved from baseline to the final follow-up time point in both groups. The ICIQ-FLUTS voiding domain score increased by a small amount across the time points in both groups; therefore, there was no evidence of an improvement in voiding in both groups and no significant differences between groups [mean difference 0.2 (95% CI −0.1 to 0.6); p = 0.142]. For the ICIQ-FLUTS incontinence domain, the scores improved at the final time point compared to baseline, indicating improvement in both groups. However, there was no evidence of significant differences between the groups [mean difference −0.2 (95% CI −0.8 to 0.4); p = 0.512]. There was a difference for the ICIQ-FLUTS filling domain score: at the final follow-up point, the effect size was significant, with a small difference favouring urodynamics [mean difference −0.44 (95% CI −0.86 to −0.03); p = 0.036] (*Table 8*). This may indicate better filling-phase symptoms (such as urgency) in the urodynamics arm, but the level of certainty and the clinical significance are debated, especially since similar results were not shown when analysing the urgency perception symptom questionnaire.

International Consultation on Incontinence Questionnaire overactive bladder

ICIQ-OAB scores showed that across the trial, women in both groups reported a slight improvement in symptoms. At 3 and 6 months post randomisation, participants in the urodynamic arm reported poorer outcomes than those in the

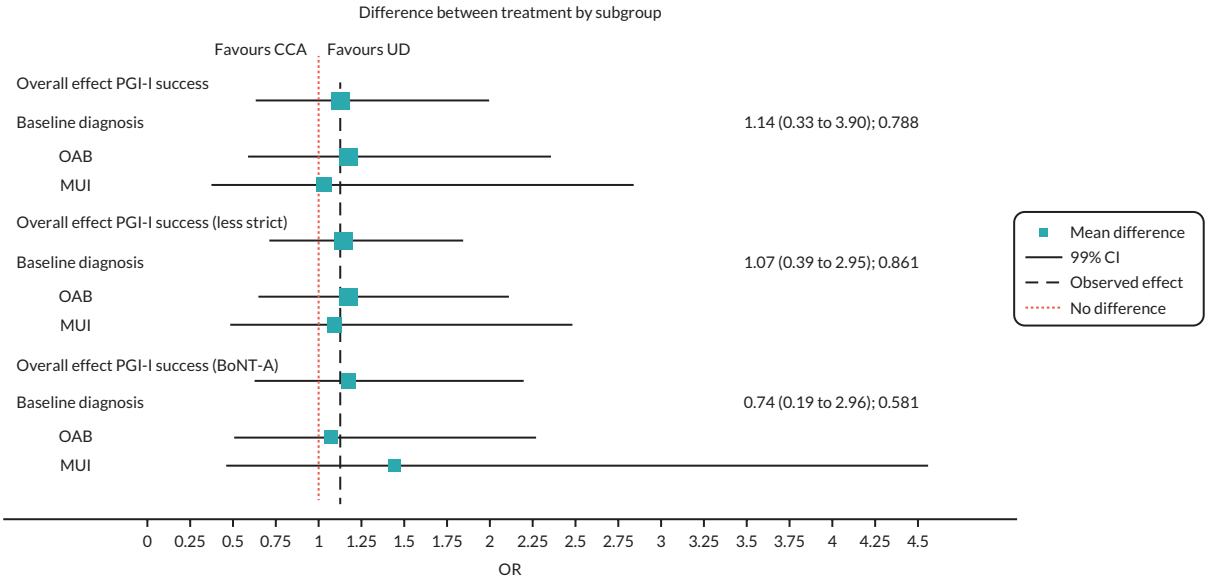

FIGURE 6 Subgroup analysis according to baseline diagnosis of OAB vs. urgency-predominant MUI at the final time point (ITT population).

TABLE 8 Secondary outcomes – ICIQ-FLUTS scores, ICIQ-OAB scores, HRQoL and urinary symptom interference (ITT population)

	Urodynamics *N* = 550	CCA only *N* = 549	Mean difference (95% CI); *p*-value
ICIQ-FLUTS filling domain score			
Baseline	8.4 (2.7); (*N* = 527)	8.4 (2.8); (*N* = 530)	
6 months	6.9 (3.3); (*N* = 379)	6.7 (3.4); (*N* = 394)	0.18 (−0.22 to 0.58); 0.374
Final follow-up	6.4 (3.1); (*N* = 347)	6.9 (3.2); (*N* = 341)	−0.44 (−0.86 to −0.03); 0.036
ICIQ-FLUTS voiding domain score			
Baseline	2.6 (2.6); (*N* = 530)	2.5 (2.3); (*N* = 536)	
6 months	2.8 (2.6); (*N* = 376)	3.1 (2.8); (*N* = 386)	−0.3 (−0.6 to 0.0); 0.078
Final follow-up	3.0 (2.7); (*N* = 353)	2.8 (2.4); (*N* = 347)	0.2 (−0.1 to 0.6); 0.142
ICIQ-FLUTS incontinence domain score			
Baseline	10.5 (4.6); (*N* = 528)	10.8 (4.3); (*N* = 527)	
6 months	8.5 (5.0); (*N* = 358)	8.1 (5.1); (*N* = 377)	0.7 (0.1 to 1.2); 0.021
Final follow-up	8.1 (5.1); (*N* = 350)	8.6 (5.1); (*N* = 345)	−0.2 (−0.8 to 0.4); 0.512
ICIQ-OAB score			
Baseline	10.0 (2.7); (*N* = 531)	10.2 (2.7); (*N* = 533)	
3 months	9.1 (3.2); (*N* = 417)	8.9 (3.5); (*N* = 431)	0.3 (−0.1 to 0.8); 0.103
6 months	8.2 (3.6); (*N* = 381)	7.9 (3.7); (*N* = 394)	0.3 (−0.2 to 0.7); 0.246
Final follow-up	7.6 (3.3); (*N* = 352)	8.1 (3.5); (*N* = 345)	−0.4 (−0.9 to 0.0); 0.063
ICIQ-LUTS HRQoL score			
Baseline	51.8 (12.1); (*N* = 497)	52.3 (12.8); (*N* = 497)	
6 months	46.6 (15.0); (*N* = 324)	45.1 (15.2); (*N* = 334)	1.1 (−0.7 to 2.8); 0.244
Final follow-up	44.2 (14.2); (*N* = 303)	44.9 (15.4); (*N* = 292)	−0.2 (−2.0 to 1.7); 0.845
EQ-5D-5L			
Baseline	0.653 (0.290); (*N* = 531)	0.674 (0.293); (*N* = 529)	
3 months	0.660 (0.293); (*N* = 434)	0.663 (0.286); (*N* = 449)	0.003 (−0.023 to 0.029); 0.840
6 months	0.674 (0.300); (*N* = 397)	0.673 (0.289); (*N* = 402)	0.011 (−0.016 to 0.038); 0.410
Final follow-up	0.669 (0.295); (*N* = 355)	0.656 (0.312); (*N* = 341)	0.015 (−0.013 to 0.043); 0.286
How much do urinary symptoms interfere with your everyday life?			
Baseline	8.0 (2.1); (*N* = 530)	7.9 (2.0); (*N* = 533)	
6 months	6.5 (3.0); (*N* = 372)	6.3 (3.1); (*N* = 375)	0.1 (−0.3 to 0.5); 0.569
Final follow-up	6.0 (3.0); (*N* = 355)	6.2 (3.0); (*N* = 341)	−0.1 (−0.5 to 0.3); 0.546

Notes

1. The summary in each cell is mean (SD); *N*.
2. How much do urinary symptoms interfere is on the scale 0–10, with a higher score indicating more interference.
3. The filling domain score is on the scale 0–16, with a higher score indicating greater symptom severity.
4. The voiding domain score is on the scale 0–12, with a higher score indicating greater symptom severity.
5. The incontinence domain score is on the scale 0–21, with a higher score indicating greater symptom severity.
6. The OAB score is on the scale 0–16, with a higher score indicating greater symptom severity.
7. The ICIQ-LUTS QoL score is on the scale 19–76, with higher scores indicating lower HRQoL.
8. The EQ-5D-5L responses are transformed onto a scale from −0.594 to 1, with higher scores indicating better HRQoL. The effect size is the adjusted mean difference obtained using a mixed-effects linear regression. Random effects (intercept) are included for centre and participant. Fixed effects are included for the treatment variable, baseline diagnosis of OAB, presence of a 24-month follow-up and time from randomisation to follow-up. The baseline outcome for each respective variable is included in the model. Dummy variables for time point and the interaction of these and the treatment variable are also included in the model to allow the adjusted mean difference at each time point to be obtained.

TABLE 8 Secondary outcomes – ICIQ-FLUTS scores, ICIQ-OAB scores, HRQoL and urinary symptom interference (ITT population) (*continued*)

CCA only arm, although the difference was only small and there was no evidence of a significant difference. At the final follow-up time point, participants in the urodynamic arm reported a slightly better outcome than those in the CCA only arm, although the wide CI indicates the difference was not significant [mean difference −0.4 (95% CI −0.9 to 0.0); $p = 0.063$] (see *Table 8*).

Urgency perception

At baseline over two-thirds of participants in each group perceived their urgency as severe. This percentage decreased over time and at the final follow-up time point, 42.3% and 42.9% of participants reported severe urgency in the urodynamics and CCA only arm, respectively, while 25.6% and 22.6% reported no/mild urgency, respectively (*Table 9*).

At the 3-month time point, significantly more participants in the urodynamics group reported urgency compared to those in the CCA only group [OR 1.62 (95% CI 1.13 to 2.33); $p = 0.009$]. However, by the final follow-up time point, the effect was not significant [OR 0.87 (95% CI 0.63 to 1.21); $p = 0.423$] (see *Table 9*).

Table 9 further describes the change in urgency from baseline. At both 3 and 6 months post randomisation, participants in the CCA only arm were more likely to report 'cure' (defined as urgency at baseline but no urgency at follow-up) or 'improvement' (defined as reduced urgency from baseline but not to the extent of reporting no urgency) in their urgency symptoms compared to the urodynamics arm. However, the OR was only significant at the 6-month follow-up time point for the 'improved' group [OR 0.64 (95% CI 0.43 to 0.94); $p = 0.022$]. At the final follow-up time point, the OR suggests participants in the urodynamics arm were more likely to be in both the 'cured' and 'improved' categories. However, the uncertainty around the OR made the difference not significant ['cured': OR 2.04 (95% CI 0.86 to 4.80); $p = 0.104$; 'improved': OR 1.12 (95% CI 0.78 to 1.62); $p = 0.532$].

Three-day bladder diary

The numbers of participants completing the bladder diaries at 6 and 15 months were slightly higher for those randomised to CCA only [172 (31.3%) and 182 (33.1%) compared to 184 (33.5%) and 198 (36.1%), respectively]. The reporting of urgency and incontinence episodes was very similar between the two groups.

At baseline, there was a higher percentage of participants in the urodynamics arm reporting a daytime frequency > 7 per day, which was also observed in the 6-month diary [72/162 (44.4%) vs. 70/180 (38.9%)]; this is also shown in a comparison of the daytime frequencies, being higher for those who received urodynamics [7.1 (SD 2.5); ($N = 162$) vs. 6.6 (SD 2.4); ($N = 180$)] and adjusted mean difference (0.5; 95% CI 0.1 to 0.9; $p = 0.023$). This is the only significant difference between the groups.

The percentage of participants reporting a nocturnal frequency > 2 per night is higher in the CCA only arm at both the 6-month [88/180 (48.9%) vs. 70/162 (43.2%)] and 15-month [94/193 (48.7%) vs. 79/177 (44.6%)] time points. This difference was, however, also seen in the baseline diary. The summary of the follow-up diaries is shown in *Table 10*.

Health-related quality-of-life measures

Neither of the disease-specific or general HRQoL assessment tools showed a significant difference between participants undergoing urodynamics plus CAA versus CCA only. The ICIQ-LUTSQoL score showed an improvement from baseline

TABLE 9 Urgency perception (ITT population)

	Urodynamics *N* = 550	CCA only *N* = 549	OR OR (95% CI); *p*-value
Urgency perception – baseline			
None	2/521 (0.4%)	5/513 (1.0%)	
Mild	10/521 (1.9%)	12/513 (2.3%)	
Moderate	156/521 (29.9%)	151/513 (29.4%)	
Severe	353/521 (67.8%)	345/513 (67.3%)	
Missing	29/550 (5.3%)	36/549 (6.6%)	
Urgency perception – 3 months			
None	15/413 (3.6%)	25/427 (5.9%)	1.62 (1.13 to 2.33); 0.009
Mild	33/413 (8.0%)	54/427 (12.6%)	
Moderate	139/413 (33.7%)	142/427 (33.3%)	
Severe	226/413 (54.7%)	206/427 (48.2%)	
Missing	137/550 (24.9%)	122/549 (22.2%)	
Urgency perception – 6 months			
None	28/464 (6.0%)	24/471 (5.1%)	1.32 (0.95 to 1.85); 0.100
Mild	62/464 (13.4%)	98/471 (20.8%)	
Moderate	158/464 (34.1%)	157/471 (33.3%)	
Severe	216/464 (46.6%)	192/471 (40.8%)	
Missing	86/550 (15.6%)	78/549 (14.2%)	
Urgency perception – final follow-up			
None	24/489 (4.9%)	15/504 (3.0%)	0.87 (0.63 to 1.21); 0.423
Mild	101/489 (20.7%)	99/504 (19.6%)	
Moderate	157/489 (32.1%)	174/504 (34.5%)	
Severe	207/489 (42.3%)	216/504 (42.9%)	
Missing	61/550 (11.1%)	45/549 (8.2%)	
Urgency change – 3 months			
Cure	12/392 (3.1%)	21/400 (5.3%)	0.51 (0.21 to 1.24); 0.138
Improved	85/392 (21.7%)	105/400 (26.3%)	0.73 (0.47 to 1.12); 0.151
No change	258/392 (65.8%)	236/400 (59.0%)	1.46 (1.01 to 2.13); 0.046
Worsened	37/392 (9.4%)	38/400 (9.5%)	0.99 (0.61 to 1.59); 0.958
New onset	1/2 (50.0%)	1/5 (20.0%)	
Missing	157/550 (28.5%)	148/549 (27.0%)	
Urgency change – 6 months			
Cure	26/444 (5.9%)	18/437 (4.1%)	1.66 (0.75 to 3.64); 0.209
Improved	134/444 (30.2%)	170/437 (38.9%)	0.64 (0.43 to 0.94); 0.022
No change	244/444 (55.0%)	213/437 (48.7%)	1.44 (1.01 to 2.07); 0.047

TABLE 9 Urgency perception (ITT population) (*continued*)

	Urodynamics *N* = 550	CCA only *N* = 549	OR OR (95% CI); *p*-value
Worsened	40/444 (9.0%)	36/437 (8.2%)	1.14 (0.71 to 1.83); 0.580
New onset		1/5 (20.0%)	
Missing	106/550 (19.3%)	111/549 (20.2%)	
Urgency change – final follow-up			
Cure	23/469 (4.9%)	13/467 (2.8%)	2.04 (0.86 to 4.80); 0.104
Improved	188/469 (40.1%)	181/467 (38.8%)	1.12 (0.78 to 1.62); 0.532
No change	219/469 (46.7%)	235/467 (50.3%)	0.84 (0.59 to 1.20); 0.339
Worsened	39/469 (8.3%)	38/467 (8.1%)	1.04 (0.65 to 1.66); 0.870
New onset		3/5 (60.0%)	
Missing	81/550 (14.7%)	79/549 (14.4%)	

Notes
1. Cure was a change from reporting urgency at baseline to no urgency at the respective follow-up point.
2. Improved was reduced urgency perception but not to the extent of reporting none.
3. No change women remained in the same urgency perception category.
4. Worsened were women reporting urgency at baseline who subsequently reported increased urgency at a follow-up point.
5. New onset was women who reported none at baseline but subsequently developed urgency.
6. The summary in each cell is count and percentage.
7. The effect size for reporting urgency perception at the three follow-up time points comes from a mixed-effects ordered logistic regression. Random effects are included for centre and participant. Fixed effects are included for the treatment variable, presence of a 24-month follow-up, time from randomisation to follow-up and baseline diagnosis of OAB. Dummy variables are also included for time point and an interaction of these and the treatment variables are included to allow the treatment effect to be estimated at each time point.
8. The second half of the table reporting change in urgency uses a mixed-effects logistic regression to obtain the effect sizes for the cure, improved, no change and worsened outcomes. Random effects (intercept) are included for centre and participant. Fixed effects are included for the treatment variable, presence of a 24-month follow-up, and time from randomisation to follow-up. Dummy variables are also included for time point and an interaction of these, and the treatment variables are included to allow the treatment effect to be estimated at each time point.

to final follow-up time point in both groups. The EQ-5D-5L had small fluctuations across time points, with no evidence of significant differences between groups (see *Table 8*).

Treatment received following randomisation

The treatment received following randomisation was guided by either the urodynamic diagnosis or the CCA only diagnosis (see www.fundingawards.nihr.ac.uk/award/15/150/05). Adherence to the treatment pathways was monitored during the QA process, which recorded two deviations (see *Chapter 7* for further details).

Table 11 shows the range of treatments received by participants following their assessment either from urodynamics or from CCA only. A slightly higher number of participants in the CCA only arm received treatment compared to those in the urodynamics arm [469 (85.4%) vs. 456 (82.9%)]. One hundred and seventy-four participants did not receive treatment from randomisation to the end of the follow-up period (94 participants in the urodynamics arm and 80 participants in the CCA arm).

The treatment received by the greatest number of women was BoNT-A in both groups (*n* = 620), with more participants in the CCA only arm receiving BoNT-A compared to those in the urodynamics arm [343 (71.6%) vs. 277 (59.3%)]. There were only 21 participants who received surgery for SUI and this was more likely amongst those randomised to urodynamics

TABLE 10 Three-day bladder diary at 6 and 15 months post randomisation (ITT population)

	Urodynamics *N* = 550	CCA only *N* = 549	Effect size (95% CI); *p*-value
Number of women who completed 6-month diary	172/550 (31.3%)	184/549 (33.5%)	
Daytime frequency	7.1 (2.5); (*N* = 162)	6.6 (2.4); (*N* = 180)	0.5 (0.1 to 0.9); 0.023
Daytime frequency > 7 per day	72/162 (44.4%)	70/180 (38.9%)	1.1 (0.5 to 2.7); 0.815
Nocturnal frequency	2.2 (1.5); (*N* = 162)	2.2 (1.4); (*N* = 180)	0.0 (−0.2 to 0.3); 0.893
Nocturnal frequency > 2 per day	70/162 (43.2%)	88/180 (48.9%)	0.7 (0.3 to 1.5); 0.353
Number of mild urgency episodes per 24 hours	1.5 (2.0); (*N* = 163)	1.3 (1.6); (*N* = 183)	0.2 (−0.2 to 0.6); 0.320
Number of moderate urgency episodes per 24 hours	3.1 (3.0); (*N* = 163)	3.3 (3.2); (*N* = 183)	−0.1 (−0.7 to 0.5); 0.710
Number of severe urgency episodes per 24 hours	1.8 (2.3); (*N* = 163)	1.8 (2.3); (*N* = 183)	0.1 (−0.4 to 0.6); 0.674
UI episodes per 24 hours	3.1 (3.0); (*N* = 163)	3.1 (3.8); (*N* = 183)	0.2 (−0.3 to 0.8); 0.415
UUI episodes per 24 hours	2.3 (2.6); (*N* = 163)	2.2 (3.0); (*N* = 183)	0.2 (−0.3 to 0.7); 0.430
SUI episodes per 24 hours	0.1 (0.2); (*N* = 163)	0.0 (0.2); (*N* = 183)	−0.0 (−0.0 to 0.0); 0.995
Number of women who completed 15-month diary	182/550 (33.1%)	198/549 (36.1%)	
Daytime frequency	6.6 (2.0); (*N* = 177)	6.5 (2.0); (*N* = 193)	0.1 (−0.3 to 0.6); 0.504
Daytime frequency > 7 per day	56/177 (31.6%)	67/193 (34.7%)	0.9 (0.8 to 1.0); 0.061
Nocturnal frequency	2.2 (1.5); (*N* = 177)	2.2 (1.3); (*N* = 193)	−0.0 (−0.3 to 0.2); 0.745
Nocturnal frequency > 2 per day	79/177 (44.6%)	94/193 (48.7%)	1.0 (0.9 to 1.1); 0.815
Number of mild urgency episodes per 24 hours	1.6 (2.2); (*N* = 179)	1.6 (1.9); (*N* = 196)	0.0 (−0.4 to 0.4); 0.895
Number of moderate urgency episodes per 24 hours	2.7 (2.5); (*N* = 179)	2.7 (2.6); (*N* = 196)	−0.1 (−0.6 to 0.5); 0.849
Number of severe urgency episodes per 24 hours	1.6 (2.5); (*N* = 179)	1.4 (2.0); (*N* = 196)	0.3 (−0.2 to 0.7); 0.263
UI episodes per 24 hours	2.8 (3.4); (*N* = 179)	2.6 (3.1); (*N* = 196)	0.1 (−0.5 to 0.7); 0.688
UUI episodes per 24 hours	2.1 (2.9); (*N* = 179)	1.7 (2.3); (*N* = 196)	0.3 (−0.2 to 0.8); 0.279
SUI episodes per 24 hours	0.0 (0.2); (*N* = 179)	0.0 (0.2); (*N* = 196)	0.0 (−0.0 to 0.0); 0.957

Notes
1. Daytime frequency > 7 and nocturnal frequency > 2 are summarised with count and percentage and the effect size is therefore an adjusted OR. The remaining outcomes are summarised with mean, SD, and count and the effect size is the adjusted mean difference.
2. Where effect sizes are presented, these are obtained from a mixed-effects, repeated-measures model. Random effects (intercept) are included for centre and participant. Fixed effects are included for receiving urodynamics, baseline diagnosis of OAB. A dummy variable is also included to differentiate between the 6- and 15-month diary and an interaction of this, and the treatment variable is included to allow the treatment effect to be estimated at both 6 and 15 months.

compared to CCA only [16 (3.4%) vs. 5 (1.0%)]. Nineteen women received SNM [11 (2.4%) vs. 8 (1.7%)] and 48 participants received percutaneous tibial nerve stimulation (PTNS) [19 (4.1%) vs. 29 (6.1%)] in both groups respectively (see *Table 11*).

The small number of women receiving PTNS (48 women), surgery for SUI (21 women) or SNM (19 women) would make comparison of outcomes by treatments recorded clinically and statistically non-meaningful. At the final time point:

- The participant-reported success rates ('very much improved' and 'much improved') in the urodynamics versus CCA only arms were 0% versus 11.5% for PTNS, 7.1% versus 20% for SUI and 20.0% versus 12.5% for SNM.

TABLE 11 Treatments received following randomisation

	Urodynamics *N* = 550 (%)	CCA only *N* = 549 (%)
Received any treatment	467 (84.9)	479 (87.2)
BoNT-A	277 (59.3)	343 (71.6)
Medication	253 (54.2)	240 (50.1)
Physiotherapy PFE with/without electric stimulation	182 (39.0)	148 (30.9)
Catheterisation	61 (13.1)	65 (13.6)
PTNS	19 (4.1)	29 (6.1)
Cystoscopy with/without cystodistention with/without urethral_dilatation	22 (4.7)	3 (0.6)
Surgery for SUI	16 (3.4)	5 (1.0)
SMN	11 (2.4)	8 (1.7)
Antibiotics	4 (0.9)	8 (1.7)
Bladder instillation	9 (1.9)	2 (0.4)
Acupuncture	1 (0.2)	8 (1.7)

PFE, pelvic floor exercises.

Note
1. Note that participants can report receiving more than one treatment.

- Using the less strict definition of success ('very much improved', 'much improved' and 'improved') the success rates increased to 27.8% versus 30.8% for PTNS, 50.0% versus 40% for SUI and 30.0% versus 50.0% for SNM, respectively.

Safety data

Serious adverse events

There were nine SAEs reported during the follow-up period by nine participants. The nine SAEs included five deaths, all of which were not related to the trial participation. Four participants experienced expected SAEs. One participant experienced general-anaesthetic-related SAE (sudden desaturation and an upper respiratory tract infection) which required monitoring of oxygen levels and antibiotics. A second participant had possible pyelonephritis and a UTI which required hospitalisation, where a kidney, ureter and bladder X-ray was performed. Two participants were required to self-catheterise following intravesical BoNT-A, which was classified by the local PI as a SAE.

Adverse events

Two hundred and thirty-five participants experienced at least one AE during the follow-up period (113 participants in the urodynamics arm and 122 participants in the CCA arm). The rates of AE were low and similar between the two groups. The most frequently occurring AEs were UTIs (80 participants; 7.3%), requirement for prophylactic antibiotics (76 participants; 6.9%) and urinary retention requiring CISC (58 participants; 5.3%). As BoNT-A was the most common treatment received by the women, AEs following BoNT-A were amongst the most commonly reported. The AEs are shown in *Table 12*.

TABLE 12 Adverse events

	Urodynamics *N* = 550 (%)	CCA only *N* = 549 (%)
UTI	39 (7.1)	41 (7.5)
Using prophylactic antibiotics	40 (7.3)	36 (6.6)
CISC required	26 (4.7)	32 (5.8)
Limb weakness after BoNT-A	8 (1.5)	16 (2.9)
Pain during BoNT-Ax	4 (0.7)	12 (2.2)
Urine retention not requiring CISC	5 (0.9)	11 (2.0)
General pain	8 (1.5)	6 (1.1)
Wound infection	4 (0.7)	9 (1.6)
Bowel problems	1 (0.2)	3 (0.5)
Tiredness	2 (0.4)	2 (0.4)
Dizziness	2 (0.4)	1 (0.2)
Worsening of existing pain	2 (0.4)	1 (0.2)
Pain during urodynamics	3 (0.5)	
Vaginal pain	1 (0.2)	1 (0.2)
Leg or back pain	1 (0.2)	1 (0.2)
Haematuria following BoNT-A	2 (0.4)	
Participant collapsing or feeling faint during urodynamics	2 (0.4)	
Burning during urodynamics	1 (0.2)	
Numb buttock following SNM	1 (0.2)	
Chest infection following surgery	1 (0.2)	
Loss of effectiveness following SNM	1 (0.2)	
General anaesthetic complication during surgery	1 (0.2)	
Dry vagina	1 (0.2)	
Urethral bulking pain	1 (0.2)	
Groin pain	1 (0.2)	
Post operative pain	1 (0.2)	
Nerve pain		1 (0.2)
Tremors		1 (0.2)
Muscle weakness		1 (0.2)
Sickness and nausea		1 (0.2)

Note
1. Note that women can report experiencing more than one adverse event.

Chapter 5 Economic evaluation

The economic evaluation was from an NHS perspective as other significant care-related contacts outside the NHS were not anticipated. Private expenditure was incorporated within a sensitivity analysis that adopts a societal perspective. The evaluation uses both a within-trial time frame and a modelled patient-lifetime time frame; the modelled analysis was the primary focus of the economic evaluation. Methods are in line with those of NICE[75] and have been previously described in the trial protocol[1] and the study Health Economics Analysis Plan (HEAP; see *Report Supplementary Material 1*); deviations from these documents are summarised in the *Discussion*.

Methods

Resource use

Participant-level data were collected for the trial interventions [urodynamics plus CCA (referred to as the urodynamics arm) and CCA only (referred to as the CCA only arm)], plus subsequent treatments, investigations and other health service contacts. Data were collected on CRFs at 6 and 15 months post randomisation via a review of participant medical records. In line with the clinical trial, a 24-month follow-up was undertaken for participants who had their treatment delayed due to the COVID-19 pandemic. Other medical care and primary care contacts were collected via participant questionnaires. Provision of incontinence pads by the NHS is not universal across the UK, but, for the purposes of the analysis, we made the simplifying assumption that they were an NHS cost. All items of resource use are shown in *Table 13*.

Costs to participants of undergoing treatment and personal expenditure on products relating to their OAB symptoms were captured by a questionnaire at baseline, 6, 15 and 24 months, where appropriate. Likewise, time taken away from work due to treatment of symptoms and reduced productivity at work due to symptoms were also recorded on the participant questionnaires.

A full list of resource use items is given in *Table 13*.

Unit costs

The principal sources of unit costs were NHS Reference Costs, the *British National Formulary* (BNF) and Unit Costs of Health and Social Care. All costs are at 2020–1 price levels. A full list of unit costs is given in *Table 13*, with further details in *Appendix 2* (*Table 31*). Costs and outcomes were discounted at 3.5% as recommended by NICE.[75]

A separate unit cost of AEs was not applied as these were identified and costed individually using the data and unit costs described above. So, for example, days in hospital, GP attendance and antibiotic prescriptions associated with AEs are included within the relevant categories of cost.

Quality-adjusted life-years

Health-related utility was assessed using the EQ-5D-5L measure at baseline, 6, 15 and 24 months post randomisation, where appropriate. QALYs were estimated using the EQ-5D-5L van Hout 'cross-walk' tariff as recommended by NICE at the time of the trial's conduct[76] using linear interpolation between the scheduled time points.

An exploratory analysis was undertaken to assess the QALY loss related to urodynamics (e.g. anxiety and discomfort) by estimating the degree to which EQ-5D-5L values at 6 months post randomisation were affected by time since urodynamic testing. If a robust estimate of QALY loss was produced, the impact of its incorporation into the cost-effectiveness analysis was examined using a sensitivity analysis. This analysis took the form of a regression using the difference between post-urodynamics and pre-urodynamics utility as the dependent variable, and time since urodynamics, its squared term, and other covariates as the independent variables. The estimated disutility associated with urodynamics was to be used as an adjustment to the QALYs of all participants undergoing urodynamics if $p < 0.1$ on either of the two time covariates.

TABLE 13 Unit costs

Item of resource use and associated care report form	Cost, £	Source[a]
Hospital visits		
Outpatient visit	161.17	NHS Reference costs 2020/2021
Ward review (not admitted)	161.17	NHS Reference costs 2020/2021
Elective hospital admission	2358.92	NHS Reference costs 2020/2021
Emergency hospital admission	509.11	NHS Reference costs 2020/2021
Investigations		
Invasive urodynamics	230.29	NHS Reference costs 2020/2021
Non-invasive urodynamics	230.29	NHS Reference costs 2020/2021
Cystoscopy	272.95	NHS Reference costs 2020/2021
MSU test	10.18	NHS Reference costs 2020/2021
Voiding assessment – catheterisation	213.28	NHS Reference costs 2020/2021
Renal ultrasound scan	64.31	NHS Reference costs 2019/2020
CT	93.94	NHS Reference costs 2019/2020
MRI	325.33	NHS Reference costs 2020/2021
BoNT-A treatment sessions[b]		
Drug costs[c]		
BoNT-A 50 unit	71.63	BNF 2021
BoNT-A 100 unit	166.00	BNF 2021
BoNT-A 200 unit	268.10	BNF 2021
BoNT-A 500 unit	308.00	BNF 2021
Cystoscope costs		
Cystoscope + general/regional	731.84	NHS Reference costs 2020/2021
Cystoscope + local/local plus sedation	272.95	NHS Reference costs 2020/2021
Other medical care and appointments		
Absorbent pads	5.00	NHS price not available. Price based on a pack of 30 pads from online search of products.
Intermittent catheter	162.12	NHS Reference costs 2020/2021
Medications	Various	NHS Business Services Authority, 2021
Bladder instillation	658.83	NHS Reference costs 2020/2021
Clinic appointment	161.17	NHS Reference costs 2020/2021
Phone call	119.21	NHS Reference costs 2020/2021
SNM procedures		
SNM + permanent + inpatient	9036.45	NHS Reference costs 2020/2021
SNM + permanent + day surgery unit	1614.97	NHS Reference costs 2020/2021
SNM + permanent + main theatre unit	1614.97	NHS Reference costs 2020/2021
SNM + not permanent + inpatient	5429.52	NHS Reference costs 2020/2021

TABLE 13 Unit costs (*continued*)

Item of resource use and associated care report form	Cost, £	Source[a]
SNM + not permanent + day surgery unit	3540.69	NHS Reference costs 2020/2021
SNM + not permanent + main theatre unit	3540.69	NHS Reference costs 2020/2021
Variable – return to theatre		
Lead removal	517.30	NHS Reference costs 2020/2021
SUI procedures		
Fascial (fascial sling)	7319.10	NHS Reference costs 2020/2021
Urethral bulking agent	321.46	NHS Reference costs 2020/2021
Primary and community care		
GP	33.00	PSSRU 2021
Practice nurse	21.00	PSSRU 2021
Physiotherapist	20.50	PSSRU 2021
Social care	23.00	PSSRU 2021
Lost productivity		
Hourly wage	18.01	Annual Survey of Hours and Earnings 2020/2021

CT, computed tomography; MRI, magnetic resonance imaging; MSU, mid-stream urine.
a Full details of unit costs, including Healthcare Resource Group codes, are given in *Appendix 2*, *Table 31*.
b BoNT-A treatments sessions are costed as the sum of two components; drug costs plus the NHS reference cost for cystoscope (general/regional or local plus sedation).
c Costs relate to the mean price across the products that are available for each dose.

Analysis

An incremental analysis was undertaken, together with plots on the cost-effectiveness plane (CEP) reflecting second-order uncertainty, and their associated cost-effectiveness acceptability curves (CEACs). Cost-effectiveness was assessed in relation to a threshold of £20,000 per QALY gained.

The following subgroup analyses, aligned with the clinical analysis, were planned:

- a comparison between participants with baseline diagnosis of OAB and urgency-predominant MUI
- a comparison between the clinical effectiveness of the different treatment pathways of those who started on BoNT-A and those who started with SNM treatment
- a comparison of the effectiveness of (1) SNM and (2) BoNT-A according to CCA only compared to treatment which was guided by urodynamics.

Deterministic sensitivity analyses were undertaken in relation to:

- complete case analysis
- societal perspective that includes patient costs and production losses
- utility loss relating to the use of urodynamics as estimated by exploratory analysis
- alternative, unpublished, cost for urodynamics taken from a UK study (personal communication)
- use of a £30,000 cost-effectiveness threshold
- use of an alternative utility tariff for the EQ-5D-5L[76,77]
- the inclusion of additional predictors within the multiple imputation.

Two frameworks were applied to provide complementary sets of analysis: firstly, a within-trial framework describing the trial results up to the 24-month follow-up; secondly, a decision-analytic model framework that supplemented the trial data with external evidence that captures clinical and patient events beyond the end of the trial.

The within-trial analysis followed the best-practice guidelines.[78] The analysis calculated total costs and QALYs for each participant and estimated the incremental costs and QALYs using a regression model with the following baseline covariates; OAB dummy, age, age squared, follow-up time, follow-up time squared, number of deliveries, urgency perception dummies, CentreNo dummies and the QALY regression additionally included baseline utility score. Missing data were imputed using age, OAB dummy, 15-month dummy, number of deliveries and urgency perception as predictors.[79,80] Costs and QALYs were calculated up to 24 months, with a dummy variable being added with a value of '1' if the participant was not followed up to 24 months, and '0' otherwise. As such, the estimated increment is assumed the same for all participants, with the coefficient on the dummy variable estimating the shortfall in costs associated with a shorter follow-up. A seemingly unrelated regression was planned, but other specifications that were better suited to the distribution of the data were also explored.[78]

The choice of regression model was based on an assessment of the distributions for the cost and QALY data and the appropriateness of the distribution family within a GLM specification. In the event of normally distributed data a seemingly unrelated regression was planned, but, if the data were skew, the most appropriate distribution family within a GLM would be assessed using the modified Park test.[81]

The data are assumed to be missing at random; that is, that the probability that data are missing is independent of unobserved values, given the observed data. The missingness is non-monotonic because those with missingness at one time point may subsequently return data at a later time point, therefore inverse probability weighting is not an appropriate method for dealing with missing data in this context. There are no statistically significant differences in missingness between arms of the trial. Based on the logistic regressions, the missingness is correlated with age, follow-up time, number of deliveries and previous therapies for both total costs and total QALYs.

The decision-analytic approach represents the primary analysis based on its recognised advantages over a purely trial-based approach.[82] Of particular importance in the context of this study is the need to consider patient costs and outcomes beyond the end of the trial. Differences in the choice of initial therapy post randomisation could generate different success rates, retreatment rates, costs and patient outcomes. Such work inevitably requires the use of external data and some assumptions; however, the uncertainty that these generate will be explored in the analysis.

The structure of the model beyond 24 months was developed after a review of economic evaluations relating to urodynamics and/or treatments for OAB or SUI. A model structure was then conceptualised that was based around the NHS treatment pathways used within the trial design (see www.fundingawards.nihr.ac.uk/award/15/150/05), but also capturing the important features of clinical management and patient outcomes identified in the review. The model structure, a hybrid model with a decision tree describing short-term events and Markov processes describing long-term events, is shown in *Figure 7*. The conceptual modelling that led to the adoption of this model structure is given in *Appendix 3*.

In short, the model takes the estimated total costs and QALYs at 24 months directly from FUTURE trial, then applies a Markov process; participants with successful treatment remain on that treatment, with treatment failures moving to 'other care'. The proportion of participants receiving BoNT-A or SNM, or having received surgery for SUI, or receiving 'other care' at 24 months is taken from FUTURE. The costs for ongoing BoNT-A, SNM replacement and SNM removals are taken from the table of unit costs (see *Table 13*), while the cost for 'other care' is estimated from FUTURE (using the observed cost of participants who have not received any of the alternative treatments). Events beyond that time point incorporated evidence drawn from a review of existing models. These reviews and the associated parameters are given in *Appendix 3*.

The model includes all-cause mortality using the UK lifetables and discounts costs and QALYs at 3.5% per annum. Utilities are not reduced to account for comorbidities associated with ageing. A half-cycle correction is applied.

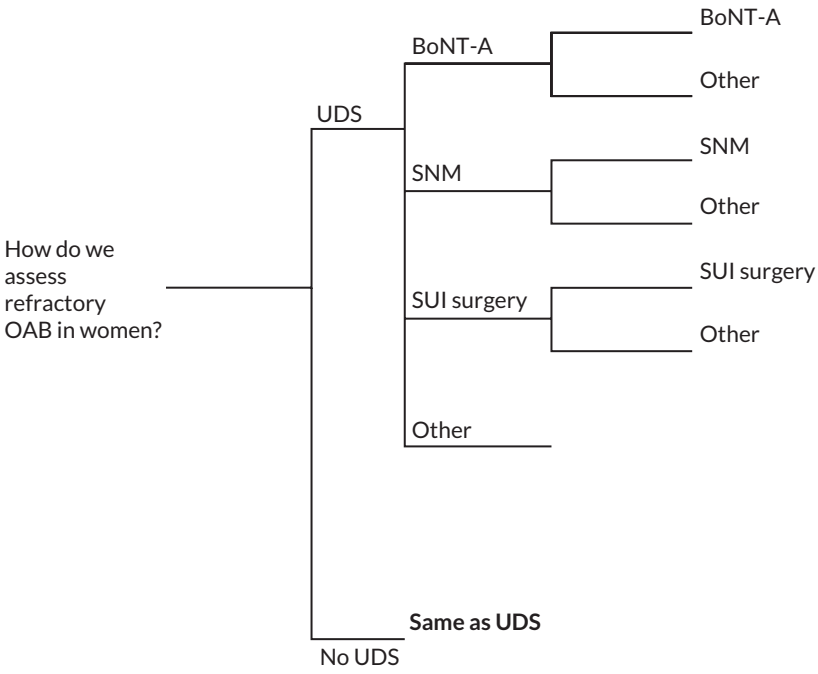

FIGURE 7 Model structure. UDS, urodynamics. The nodes immediately to the right of 'UDS' and 'No UDS' are Markov nodes, with descriptors on the far right representing transitions to the relevant Markov node. Death is included in the model but is excluded from this figure for simplicity.

A value-of-information analysis was planned in order to identify those parameters where there was greatest value in resolving outstanding uncertainty. This was to use the Sheffield Accelerated Value of Information tool, an annual patient population of 77,000 women,[25,48] and a 10-year time horizon.[83]

Results

Costs

A description of the resources used by participants across the full follow-up period (which can be 15 or 24 months), without imputation, is given in *Table 14*. This shows that not all participants randomised to urodynamics received the intervention, while a small number of participants who were randomised to CCA only received urodynamics, although overall participants in the intervention arm received more urodynamic testing. The urodynamics arm also received more clinic visits (0.70 vs. 0.45) and more procedures relating to SUI (0.03 vs. 0.01). All other differences are not statistically significant.

When combined with the unit costs from *Table 13* and *Appendix 2*, the distribution of costs across participants is highly skewed, with the vast majority having costs below £5000, but with smaller numbers having costs stretching up to around £20,000 (*Figure 8*). The disaggregated costs mirror the resource-use findings, with statistically significant differences limited to urodynamic visits, clinic visits and procedures related to SUI (*Table 15*).

Based on the distribution of costs, a GLM was adopted, with the modified Park test indicating that a gamma family and identity link was most appropriate to model total costs and estimate the differences (increment) between the two trial arms. Analysis was undertaken for all participants, assuming the same increment across all participants regardless of length of follow-up but presented in terms of estimated 24-month costs for consistency. For the primary analysis, which takes an NHS perspective and incorporating multiple imputation, the urodynamics arm has mean costs that were £463 higher (95% CI £48 to £877), as shown in *Table 16*.

TABLE 14 NHS resource use over full follow-up (15- and 24-month participants)

	Urodynamics		CCA only			
	Mean (SD)	*N*	Mean (SD)	*N*	Difference	95% CI
Urodynamic visits	0.89 (0.31)	544	0.01 (0.10)	548	0.88	0.85 to 0.91
Clinic visits	0.70 (0.46)	550	0.45 (0.50)	549	0.25	0.19 to 0.30
BoNT-A visits	0.68 (0.83)	550	0.85 (0.80)	549	−0.17	−0.26 to −0.07
SNM appointments	0.06 (0.56)	550	0.02 (0.24)	549	0.04	−0.01 to 0.09
SUI procedures	0.03 (0.17)	550	0.01 (0.09)	549	0.02	0.00 to 0.04
Investigations[a]	0.97 (1.57)	550	0.90 (1.40)	549	0.07	−0.11 to 0.25
Other medical care[b]	49.41 (40.50)	360	51.05 (44.18)	355	−1.64	−7.87 to 4.59
Primary, community and social care visits[c]	3.66 (5.20)	310	3.51 (4.42)	311	0.15	−0.61 to 0.91
Societal resource use[d]	1.27 (1.26)	550	1.25 (1.20)	549	0.02	−0.12 to 0.16

a Includes cystoscopy, mid-stream urine, voiding assessment, ultrasound scan, CT scan and MRI.
b Includes absorbent pads, intermittent catheter, other hospital visits and medication (Vesicare, Toviaz, tolterodine, duloxetine, oxybutynin, trospium, kentera, betmiga, antibiotics for UTIs). Note intermittent catheter is assumed to be used at a rate of one per week since previous time point, or since time of operation if an operation occurred since the previous time point.
c Includes GP, nurse physiotherapist and social care appointments.
d Includes private healthcare, over-the-counter treatments, other non-NHS healthcare costs, and costs of travelling to GP, nurse, NHS physiotherapy and private healthcare appointments.

Outcomes

Mean utilities for participants across the full follow-up period (which can be 15 or 24 months post randomisation), without imputation, are shown in *Figure 9* and *Table 17*. Mean utilities are similar for all time points except for those collected at the 24-month visit, at which there is a difference of 0.078, although there are no statistically significant differences at any individual time point. When modelled with imputation, a small but not statistically significant difference in QALYs of 0.011 (95% CI −0.044 to 0.065) is estimated in favour of the urodynamics group (*Table 18*).

Cost-effectiveness

Based on the estimated incremental costs and QALYs of urodynamics (£463 and 0.011, respectively), the ICER is £42,643 per QALY gained. The CEP in *Figure 10* has a red dot, the central estimate of incremental costs and QALYs from the analysis; urodynamics produces higher costs and higher QALYs. The ellipses represent the joint uncertainty around these estimates; there is a 50% chance that the true estimate sits within the dashed ellipse, for instance. If we want to be 95% certain of the area in which the true estimates sit, we have to accept the possibility that urodynamics could lie in any of the four quadrants of the plane (i.e. higher or lower costs, together with higher or lower QALYs).

A CEAC can be derived from those same data which attaches a probability to our estimate being below any given ICER. Shown in *Figure 11*, the CEAC indicates that urodynamics has a 34% probability of being cost-effective at £20,000 per QALY gained (see *Figure 11*).

Subgroup analysis

When examining participants with a pre-randomisation clinical diagnosis of OAB and urgency-predominant MUI separately, the two groups of participants are found to have similar costs. However, participants with a diagnosis of urgency-predominant MUI have a notably greater gain in QALYs associated with urodynamics (0.053 vs. −0.010). This leads to a lower ICER than the full trial population (£8357 per QALY gained) and a commensurately higher probability

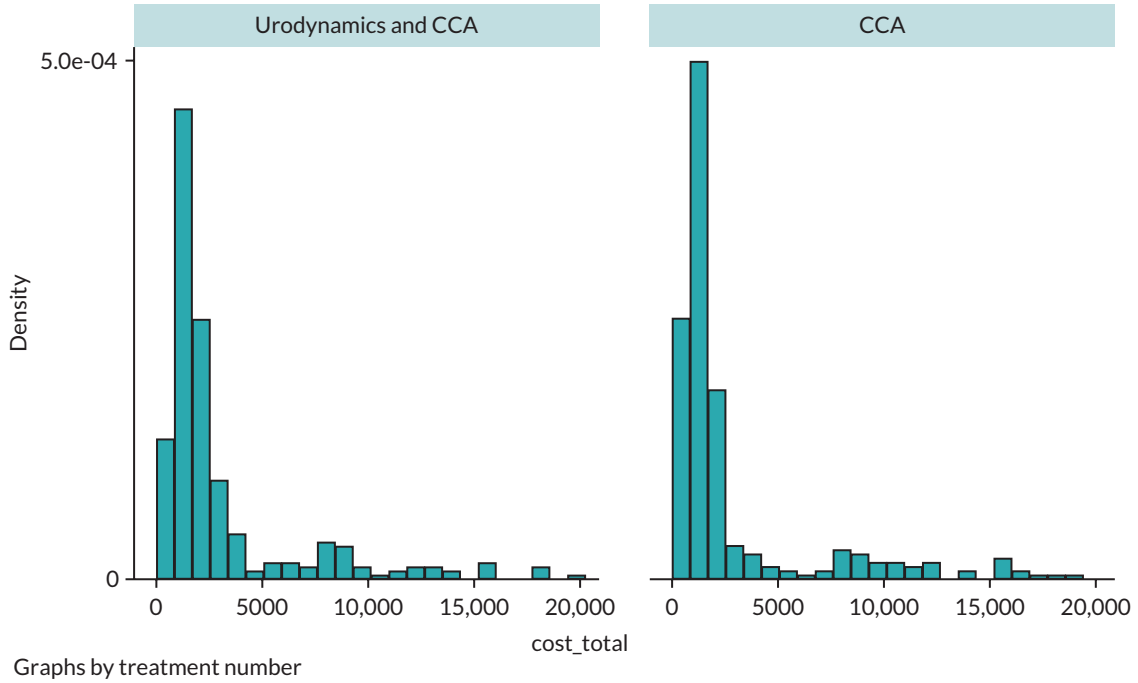

FIGURE 8 Histogram of observed total costs by arm over full follow-up (15- and 24-month participants).

TABLE 15 Disaggregated costs over full follow-up (15- and 24-month participants), by arm

	Urodynamics			CCA only				
	Mean	(SD)	*N*	Mean	(SD)	*N*	Diff	95% CI
Urodynamics	205.14	71.63	544	2.521	23.99	548	202.62	196.26 to 208.97
CCA	161.41	105.40	546	106.20	114.79	535	55.21	42.05 to 68.37
BoNT-A	337.69	428.86	550	418.39	418.86	549	−80.70	−130.90 to 30.53
SNM	11.66	193.73	550	18.84	231.54	549	−7.18	−32.45 to 18.09
SUI procedures	61.31	654.78	550	2.30	26.89	549	59.01	4.12 to 113.90
Investigations	146.39	222.90	550	131.97	216.85	549	14.42	−11.61 to 40.45
Other medical care	1861.93	3196.90	360	1976.88	3508.54	355	−114.49	−607.99 to 378.10
Primary, community and social care visits	96.82	139.11	310	93.94	118.75	311	2.88	−17.51 to 23.27
Societal costs	50.74	137.52	313	102.89	555.36	314	−52.15	−115.65 to 11.36

of being cost-effective at £20,000 per QALY (72%), as shown in *Table 19*. For participants in the OAB subgroup, urodynamics is dominated by the CCA only group (with higher mean costs and lower mean QALYs).

A relatively small number of participants received PTNS (47 participants), surgery for SUI (21 participants) or SNM (19 participants); hence, a clinical and cost-effectiveness comparison of outcomes would be non-meaningful and was therefore not undertaken.

TABLE 16 Estimated total costs over 24 months, by arm[a]

	Urodynamics		CCA only				
	Mean	(SE)	Mean	(SE)	*N*	Diff	95% CI
Total cost – complete case	4827.39	493.91	4442.66	455.39	590	384.73	54.42 to 715.03
Total cost – multiple imputation	3907.33	466.02	3444.78	449.79	1099	462.55	48.10 to 877.01

a Mean total costs were derived from the predicted values of a GLM with gamma family and identity link functions, adjusted to represent 24 months using the margins/mimrgns postestimation command in STATA-17. The difference in total costs and associated CIs are taken from the model coefficient on the randomised group dummy.

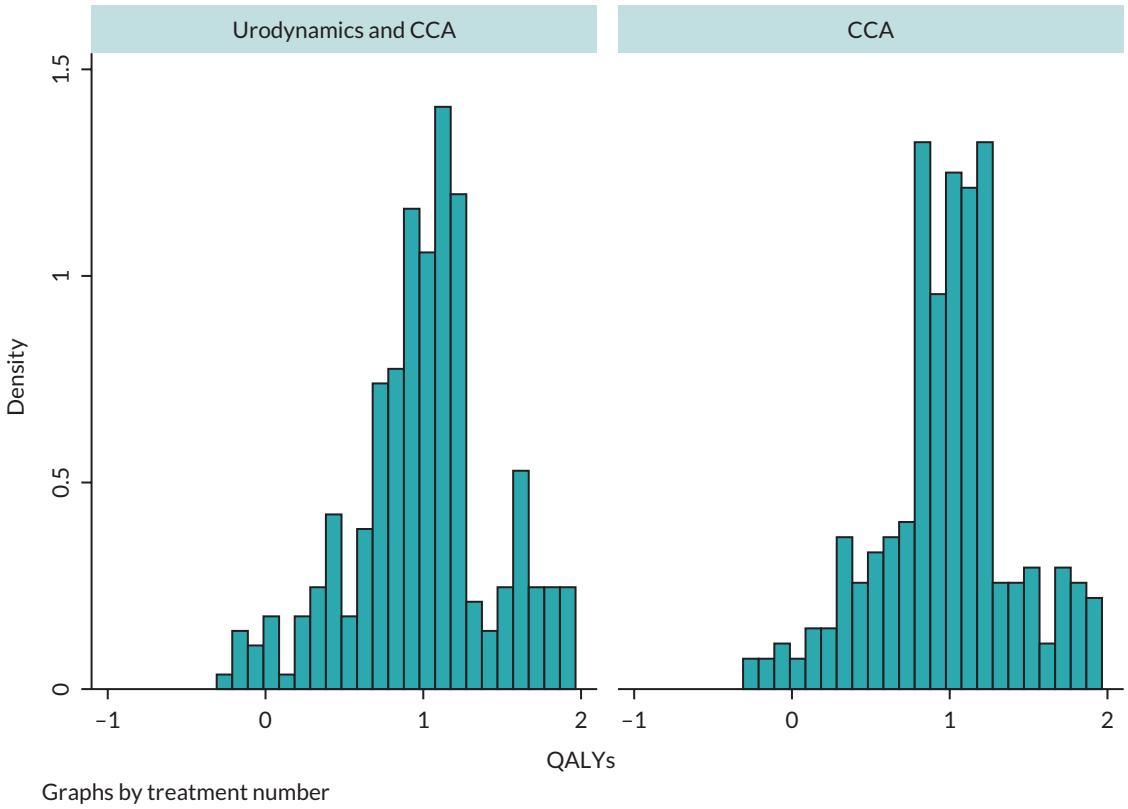

FIGURE 9 Histogram of observed QALYs over full follow-up (15- and 24-month participants), by arm.

TABLE 17 Utilities at each time point, and total QALYs over full follow-up (15- and 24-month participants), by arm

	Urodynamics		CCA only			
	Mean (SD)	*N*	Mean (SD)	*N*	Difference	95% CI
Baseline	0.653 (0.290)	531	0.674 (0.293)	529	−0.020	−0.055 to 0.016
3-month visit	0.660 (0.293)	434	0.663 (0.286)	449	−0.003	−0.041 to 0.035
6-month visit	0.674 (0.300)	397	0.673 (0.289)	402	0.001	−0.039 to 0.043
15-month visit	0.667 (0.304)	353	0.665 (0.306)	357	0.002	−0.043 to 0.047
24-month visit	0.703 (0.257)	104	0.624 (0.306)	95	0.078	−0.001 to 0.158

TABLE 18 Estimated QALYs over 24 months, by arm[a]

	Urodynamics		CCA only				
	Mean	(SE)	Mean	(SE)	*N*	Difference	95% CI
Total QALYs – Complete case	1.322	0.072	1.293	0.072	562	0.029	−0.011 to 0.069
Total QALYs – multiple imputation	1.315	0.057	1.304	0.056	1099	0.011	−0.044 to 0.065

a Quality-adjusted life-year results were derived from a GLM with Gaussian family and identity link functions. Means and associated standard errors were obtained using the margins/mimrgns postestimation command in STATA. The difference in total QALYs and associated CIs are taken from the model coefficient on the randomised group dummy.

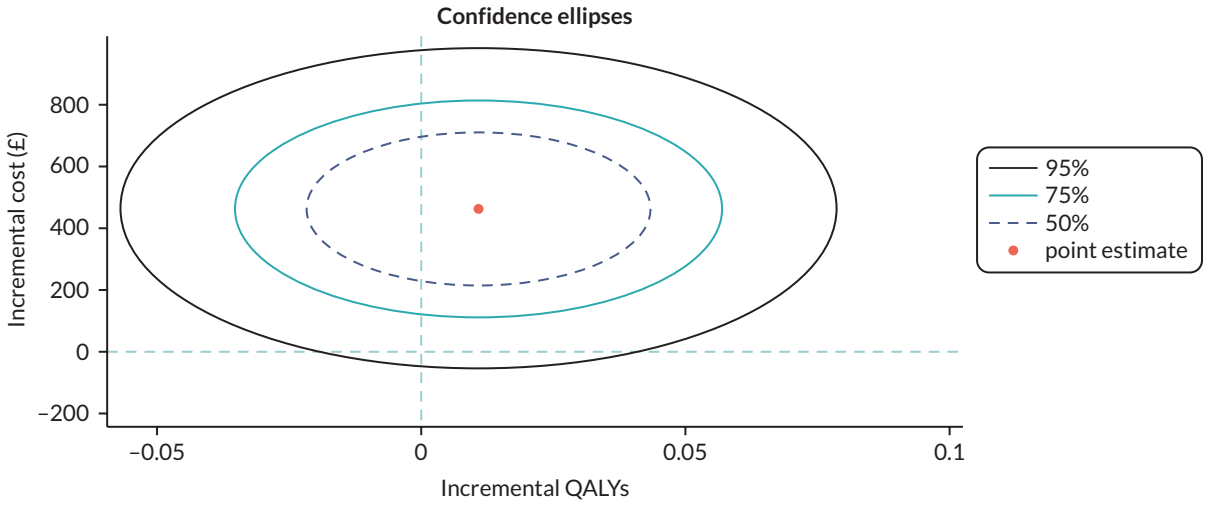

FIGURE 10 Cost-effectiveness plane for primary analysis, urodynamics vs. CCA.

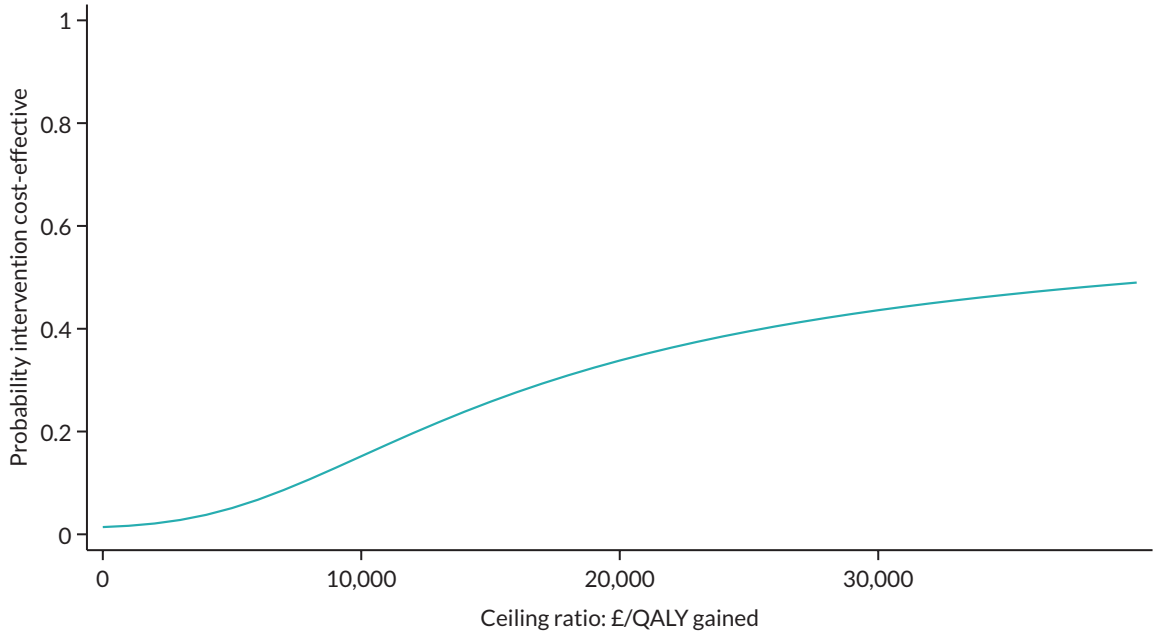

FIGURE 11 Cost-effectiveness acceptability curve (CEAC).

Sensitivity analysis

When a complete-case analysis is undertaken, the estimated incremental costs reduce to £385 and the incremental QALYs increase to 0.029 (*Table 20*). Neither of these differences is statistically significant (see *Table 18*). This leads to a lower ICER than the primary analysis of £13,281 and a higher probability of being cost-effective of 67%.

When a societal perspective is taken, there are very few changes from the primary analysis, with an ICER of £33,528 per QALY gained, associated with a probability of being cost-effective at £20,000 of 40%. When a cost-effectiveness threshold of £30,000 per QALY is used, the baseline analysis indicates that urodynamics has a 45% chance of being cost-effective.

An analysis to estimate the QALY loss related to urodynamics showed no difference in pre- and post-urodynamic EQ-5D-5L scores (see *Appendix 4*). Consequently, the QALYs for participants receiving urodynamics were not adjusted to account for any HRQoL impact of testing.

TABLE 19 Subgroup analyses

	Urodynamics		CCA only		Incremental			
	Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER	Probability that UDS is cost-effective at £20,000 per QALY gained, %
OAB	3887.49 (481.06)	1.287 (0.059)	3421.71 (454.96)	1.298 (0.059)	465.78 (262.68)	−0.010 (0.034)	−44,382.92	26.05
MUI	3958.75 (525.98)	1.369 (0.063)	3505.61 (501.84)	1.316 (0.060)	453.15 (360.71)	0.053 (0.050)	8562.84	71.73

TABLE 20 Sensitivity analyses based on estimated total costs and QALYs over 24 months

	Urodynamics		CCA only		Increment			
	Cost	QALYs	Cost	QALYs	Cost	QALYs	ICER	Probability that UDS is cost-effective at £20,000 per QALY gained, %
Baseline analysis	3907.33 (466.02)	1.315 (0.057)	3444.78 (449.79)	1.304 (0.056)	462.55 (210.94)	0.011 (0.028)	42,642.60	33.82
Complete-case analysis	4827.39 (493.91)	1.322 (0.072)	4442.66 (455.39)	1.293 (0.072)	384.73 (168.52)	0.029 (0.020)	13,280.56	67.26
Societal perspective	4127.82 (527.80)	1.315 (0.057)	3761.55 (518.84)	1.304 (0.056)	366.27 (208.06)	0.011 (0.028)	33,528.31	40.07
Alternative UDS cost[a]	3780.86 (501.94)	1.315 (0.057)	3443.36 (499.86)	1.304 (0.056)	337.50 (223.45)	0.011 (0.028)	30,953.19	42.03
Using Hernandez EQ5D mapping	3907.33 (466.02)	1.321 (0.055)	3444.78 (449.79)	1.310 (0.055)	462.55 (210.94)	0.011 (0.027)	43,120.85	33.72
Multiple imputation sensitivity analysis	3870.93 (524.33)	1.282 (0.058)	3503.31 (505.41)	1.273 (0.058)	367.62 (220.93)	0.009 (0.030)	40,097.328	38.58

UDS, urodynamics.
a Alternative UDS cost of £128.68, based on bottom-up pricing from an unpublished UK study (corresponding author Tara Homer) and inflated to 2020–1 prices.

Modelling

Using the results of the within-trial analysis as a starting point, combined with data on the women's treatment and utilities at 24 months, the model was parametrised (see *Appendix 3*, *Table 40*). The projected movement of women between treatments beyond the end of the trial is shown in the Markov traces in *Figure 12*. The four lines show the proportion of women, by year, who are assigned the costs and QALYs relating to BoNT-A, SNM, SUI, other treatments or death. This shows women moving from BoNT-A and SNM onto 'other' treatment for the first 5 years after the trial (see *Figure 12*). Beyond that point, the increasing mortality seen with ageing in the general population becomes the dominant factor (noting that the starting age for the modelled cohort, which is based on FUTURE, is 60 years). This is a natural consequence of the model structure, which directs all women to 'other care' after failure of the treatment that they are receiving after 2 years (as shown in *Figure 7*). The Markov traces in *Figure 12* also highlight an important feature of the evidence used to extrapolate the results of the trial, namely, that those women who have successful treatment for 5 years continue treatment indefinitely; this is responsible for the 'kink' in the BoNT-A traces. *Figure 12* also highlights two important results from the trial, which are: (1) urodynamics is associated with a lower rate of BoNT-A use at 24 months (which translates to the start of the Markov model) and (2) the rates of SNM and surgery for SUI at 24 months are very low.

When costs and QALYs are calculated, the lifetime analysis shows that the urodynamics group remains more costly but is now also associated with fewer QALYs than the CCA only group. As such, urodynamics is dominated by the alternative, with only a 23.4% chance of being cost-effective (*Table 21*, *Figure 13*). This is a consequence of the urodynamics arm producing a lower proportion of participants on BoNT-A (which has a higher mean utility than the alternatives) and consequently a higher proportion of participants on 'other treatments' (which has a high cost and a lower mean utility).

When the MUI subgroup is modelled over the lifetime of women, an alternative parameterisation is adopted using the within-trial and 24-month treatments/utilities for the sub-group (see *Appendix 3*, *Table 40*). Three points to note with this parameterisation are that, first, when entering the model at 24 months, women have higher QALYs in the urodynamics group (as already shown). Second, the distribution of women across treatments at 24 months is similar to that in the primary analysis (albeit with slightly fewer women receiving BoNT-A in the urodynamics group than before). Third, the utility of women receiving 'other treatments' is higher than that of women receiving BoNT-A, although this is not a statistically significant difference.

As a consequence of the second point above, the Markov traces for the MUI subgroup are similar to those of the primary analysis. As a consequence of the third point, the urodynamics group gains more QALYs than the CCA group, albeit at a higher cost. The ICER for urodynamics is £26,462 (*Table 22*).

The CEAC associated with this analysis is shown in *Figure 14*. It shows the probabilities of urodynamics being cost-effective at £20,000 and £30,000 per QALY gained as 45.3% and 53.8%, respectively.

Discussion

The primary, model-based economic analysis shows that urodynamics has a low probability of being cost-effective at £20,000 per QALY gained (23.4%), producing modestly higher costs (£1380) and slightly lower QALYs (−0.002) per patient. There are no major differences in the pattern or costs of subsequent treatments. In the subgroup of women who had a preliminary diagnosis of MUI prior to randomisation, urodynamics generates an ICER of £26,462 and a higher probability of being cost-effective (45.3%), which increases to 53.8% when a threshold of £30,000 is used.

The ICER from the trial analysis suggests that urodynamics is not cost-effective due to a modest incremental cost and a small and uncertain gain in QALYs. The sensitivity analysis shows that when a complete-case analysis is undertaken, urodynamics appears cost-effective. The reasons for this are unclear, as a sensitivity analysis that used additional predictors had little effect on the results. The impact of the pandemic on missing data, treatment patterns and, by implication, costs and QALYs could be a factor. However, initial explorations of this did not reveal any clear systematic

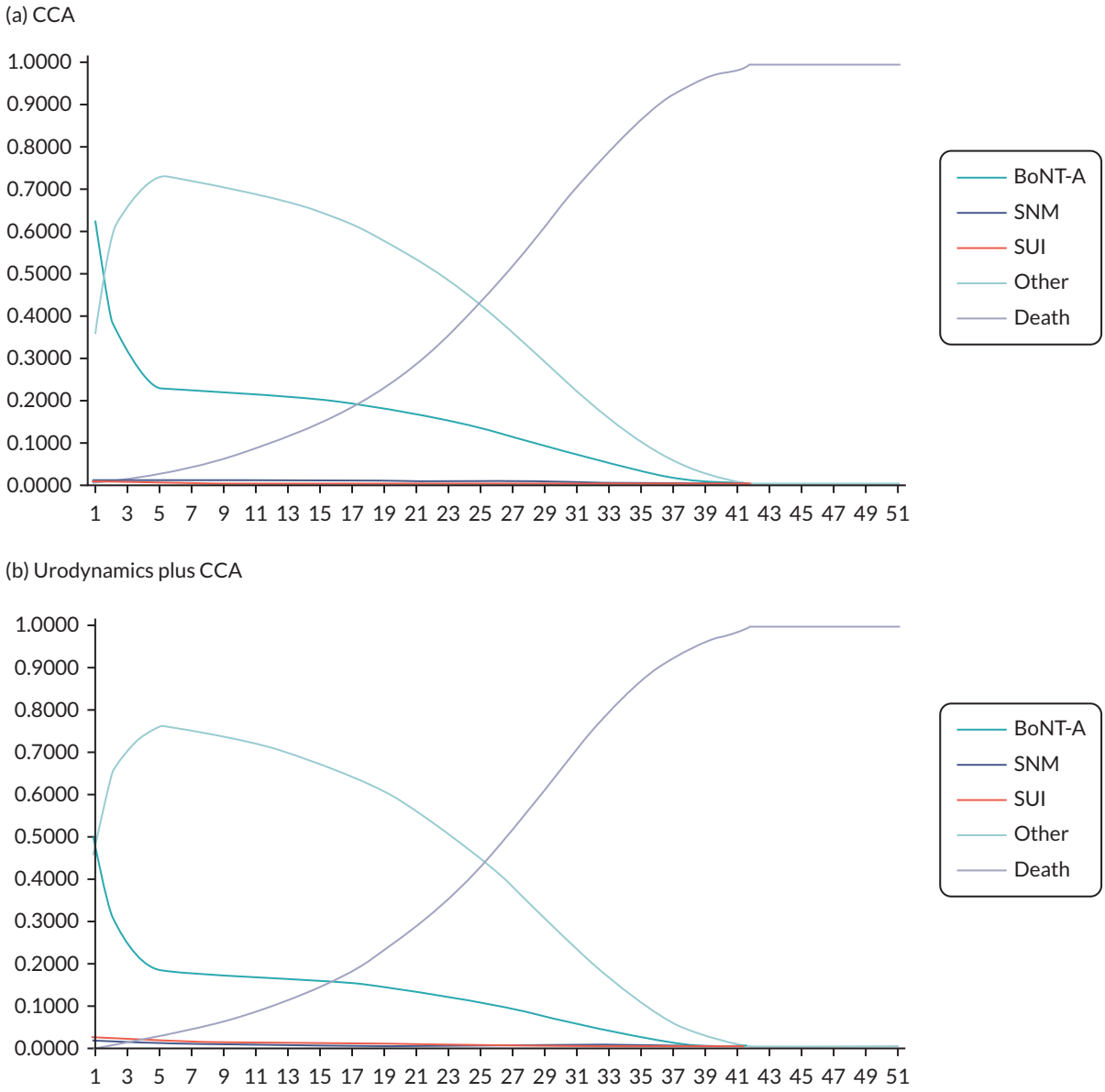

FIGURE 12 Markov traces for the two patient groups. (a) CCA. (b) Urodynamics plus CCA.

TABLE 21 Lifetime modelled cost-effectiveness of urodynamics and CCA

	Within-trial costs (£)	Long-term costs (£)	Total costs (£)	Within-trial QALYs	Long-term QALYs	Total QALYs	ICER (£ per QALYs gained)	Probability. Cost-effective at £20,000 per QALY gained, %
Urodynamics	3907	33,911	37,818	1.315	9.930	11.245		23.4
CCA	3445	32,993	36,438	1.304	9.943	11.247		76.6
Increment			1380			−0.002	Dominated	

impact. Likewise, urodynamics appears cost-effective in participants with an initial diagnosis of urgency-predominant MUI, principally due to the higher QALY gains in that group compared to participants with an initial diagnosis of OAB.

There are several issues that require further consideration when interpreting these results. First, when assessing different model specifications, it was noted that the estimated incremental costs and QALYs were sensitive to the choice of covariates and predictors for imputation. The variables used within the analysis are aligned with those used

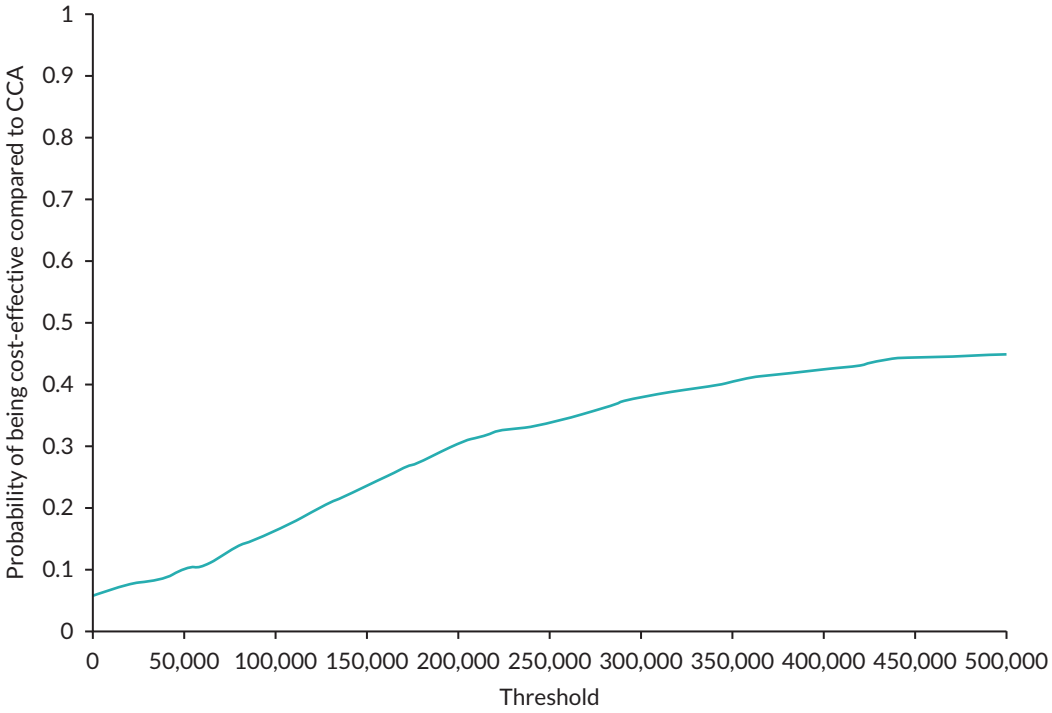

FIGURE 13 Cost-effectiveness acceptability curve for the two participant groups.

TABLE 22 Lifetime modelled cost-effectiveness of urodynamics and CCA in the MUI subgroup

	Within-trial costs (£)	Long-term costs (£)	Total costs (£)	Within-trial QALYs	Long-term QALYs	Total QALYs	ICER (£ per QALYs gained)	Probability that UDS is cost-effective at £20,000 per QALY gained, %
Urodynamics	3959	34,910	38,869	1.369	10.229	11.598		45.3
CCA	3506	33,802	37,307	1.316	10.223	11.539		54.7
Increment			1562			0.059	26,462	

in the clinical analysis in order to produce results that are consistent across the two parts of the evaluation. Alternative specifications can alter the results and conclusions; however, the relative validity of those results is unknown.

Second, the incorporation of the 24-month data into the overall analysis for a subset of participants needed to be accounted for within the statistical model used to estimate the incremental effects. The chosen pre-specified analysis was to add a dummy variable relating to not receiving a 24-month questionnaire; this assumes that the incremental costs and QALYs between the treatments are the same at 15 and 24 months. We have not formally tested this assumption, or explored alternative model specifications that could be adopted if the validity of that assumption was called into question. While including a *time × increment* interaction in the cost and QALY regressions is straightforward, we need to be wary of potential confounding effects (e.g. if delays were not consistent across recruiting sites or if they inadvertently led to prioritisation of treatment for some participants based on clinical history or prognosis). Consequently, as well as modelling a simple interaction, we may want to consider factoring in site and participant effects that help to explain how incremental costs and QALYs change between 15 and 24 months.[84]

Third, while there is good evidence that the EQ-5D-5L is sensitive to changes in severe OAB, it performs less well in milder cases.[84] As such, it may underestimate the benefits of treatments. An alternative approach would be to use a condition-specific utility measure, such as the OAB-5D,[84] but such measures are not widely accepted due to issues of

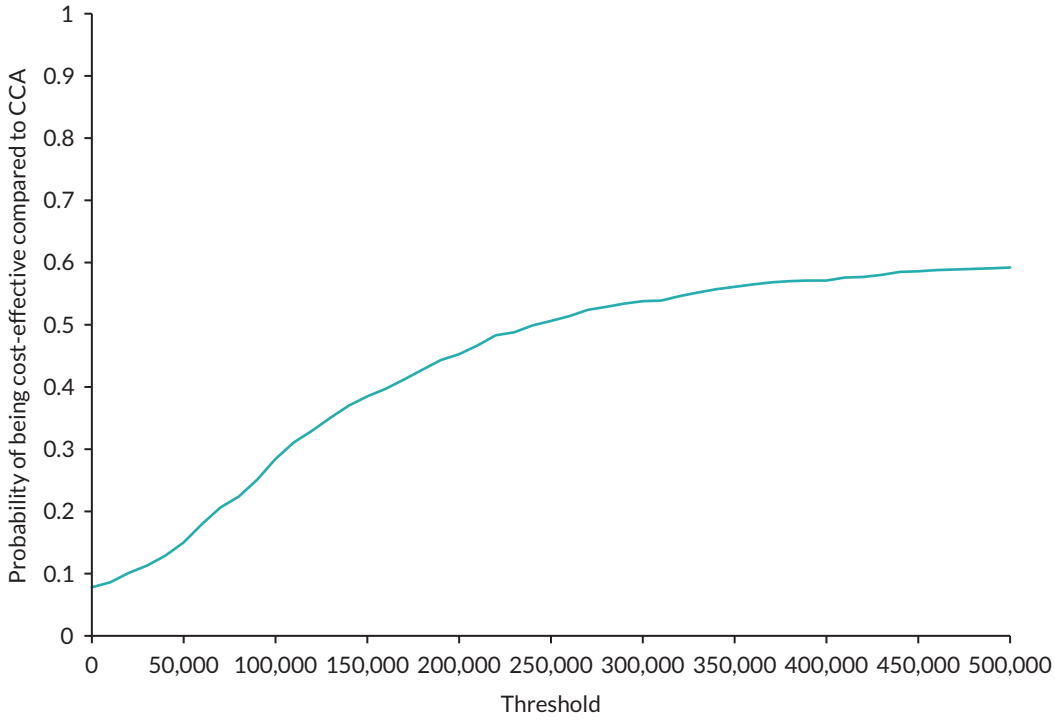

FIGURE 14 Cost-effectiveness acceptability curves for the MUI subgroup.

validity and comparability.[85] Likewise, the timing of data collection may not coincide with AEs, and so the full effect of these may not be fully captured. However, the weaknesses relating to our measurement of utility are not considered important given the clinical and economic findings; more specifically, the decision uncertainty is low.

Fourth, the perspective on costs in the primary analysis is the NHS perspective. While NICE requires an NHS and Personal Social Services perspective, the literature suggests that publicly funded care outside the NHS is extremely limited.[86,87] Private expenditure is much more significant,[86,87] and we have attempted to capture this within our societal perspective by the inclusion of patient-reported private expenditures.

The modelling of a lifetime horizon suggests that the urodynamics group is not cost-effective. This result is not unexpected given the trial results, the distribution of participants across treatments at 24 months and the structure/parameterisation of the model. The modelling makes urodynamics even less cost-effective due to fewer participants receiving BoNT-A (which has a high utility) and more women receiving 'other care' (which is costly).

There are several aspects of this analysis that need further consideration: firstly, the appropriateness of the model structure. While the chosen model structure is consistent with other previous studies, it is recognised that it is relatively simple, with no further lines of therapy beyond those observed at 24 months (except for transitions to 'other care'). Other lines of therapy could be added to all four of the health states shown in *Figure 7*; however, the evidence base for the effectiveness and HRQoL of women following these treatments after previous treatments for refractory OAB symptoms is weak (as evidenced by the need for this trial).

Second, the parameterisation imposes an implicit assumption that all treatments beyond 24 months are equally effective, regardless of how women came about receiving them; success rates and HRQoL are the same for both groups of women. However, it is possible that the lower proportion of women receiving BoNT-A in the urodynamics arm could be due to the treatment being more appropriately targeted at women, and as such it could be that participants receiving BoNT-A after a urodynamic assessment have higher success rates and HRQoL. Arm-specific utilities could be used in the model, although sample sizes become prohibitively small for some treatments. Robust estimates of 'arm-specific' long-term success rates are not thought to be available.

Third, there is an inconsistency in the way that costs are estimated for the four health states shown in *Figure 7*, which may produce a bias against urodynamics. The costs for ongoing successful treatment are based solely on the treatments: the drug and visits for BoNT-A, revision and removal for SNM, and zero ongoing cost after SUI surgery. For women who are in the 'other care' health state (either after treatment failure or not having any treatment), their costs are based on those observed in FUTURE, which includes all care costs, including follow-up visits, medications and catheterisations. This inconsistency is due to a difficulty in identifying these ongoing costs in participants who are undergoing successful treatment in FUTURE; if this could be done, we could add in these costs to the other treatment options. Our inability to do this creates a potential bias against urodynamics because women transition to 'other care' (and its high costs) more quickly due to the lower proportion of women who receive BoNT-A in that group.

Fourth, the model is constrained by the evidence base on which it is built, which is heavily reliant on patient cohorts that do not match the focus of FUTURE. It should also be noted that our review of models and parameters was not systematic; however, the sources for our long-term treatment effectiveness parameters were reviewed by clinical experts. Consequently, it seems unlikely that we have missed any large, high-quality studies in our reviews. We feel that the greatest uncertainty over the validity of the available long-term estimates is in differences in patient characteristics within the cohorts, which will be brought about by differences in the assessment of refractory OAB and differences in the treatment pathways that lead to that diagnosis. Differences in the assessment of treatment success between studies/countries are also expected to have a significant impact on results and, as such, the validity of the estimates we have used.

An exploratory analysis was undertaken to examine whether there was any evidence of a QALY loss related to participants undergoing urodynamics. We examined this by looking at the change in EQ-5D-5L between pre- and post-urodynamic trial visits. Due to the timing of urodynamics and trial visits, the post-urodynamic EQ-5D-5L responses were rarely within 1 week of the intervention. We tried to take account of this by using two time-based covariates, but it is likely that the study results are dominated by observations that sit well outside the time frame during which any HRQoL impact of urodynamics persists. Limiting the sample to participants with much shorter pre–post time differences is possible, but the choice of that time period is subjective. Any identification of a disutility associated with urodynamics also requires the selection of a time period over which it extends in order to produce a QALY decrement, which is also subjective. However, the incorporation of any QALY decrement associated with the actual urodynamics procedure will necessarily increase the ICER for the urodynamics group (thereby making it less cost-effective).

Finally, the value-of-information analysis was not undertaken at this time as an extension study is under way, which will make the results based on this study obsolete. In effect, the decision about which further studies should be funded has already been made, and the next funding decision should be made after the results of that are known and incorporated into a value-of-information analysis at that time.

Conclusion

In the primary analysis, which models the results over a lifetime horizon, the cost-effectiveness of urodynamics is reduced further, such that there is only a 23.4% chance of it being cost-effective. This further deterioration is due to the lower rate of BoNT-A use at 24 months in the urodynamics arm, which leads to fewer QALYs and higher costs for other care, relative to the CCA only arm. In the subgroup of women who had a preliminary diagnosis of MUI, urodynamics generates an ICER of £26,462 with the probabilities of being cost-effective at £20,000 and £30,000 per QALY gained being 45.3% and 53.8%, respectively.

The model structure and the parameterisation of the long-term effectiveness of treatments are necessarily simplistic due to the lack of robust, long-term data relating to this patient population. We also identified a potential bias in one of the key model inputs – the annual cost of other treatments – which we could not resolve or quantify. While this is unlikely to be important for the primary analysis, given that urodynamics is not cost-effective at 24 months, it is likely to be important for the MUI subgroup, for which urodynamics is cost-effective at 24 months and is borderline cost-effective over the patient lifetime.

Within the trial, urodynamics is shown to be more costly, principally due to the intervention itself and more clinic visits. There is evidence of greater numbers of interventions for SUI in participants undergoing urodynamics, but all other effects are highly uncertain, and not statistically significant. There is no clear evidence of differences in HRQoL (as measured by the EQ-5D-5L) at any time point, nor in total QALYs. The higher mean costs and QALYs lead to urodynamics not being cost-effective at a funding threshold of £20,000 per QALY gained, with only a 34% chance of it being cost-effective. However, this is sensitive to imputation, with the complete-case analysis showing a 67% chance of urodynamics being cost-effective. The subgroup analysis suggests larger health benefits for participants with an initial diagnosis of urgency-predominant MUI, which is associated with a 72% chance of cost-effectiveness.

Further analysis of the effects that the 24-month data have on the results is warranted, as this leads to two methodological uncertainties. First, the pattern of missing data and its impact on costs and outcomes is more complex than is generally the case in RCTs. Second, the incorporation of both 15-month and 24-month data in the estimation of total costs and QALYs is based on a simple, additive specification. Alternative approaches to these issues are possible and need consideration.

Chapter 6 Qualitative study

Qualitative studies have been widely used in healthcare research to explore patient and provider perspectives of services and evaluate various healthcare experiences.[88] The FUTURE RCT included an embedded qualitative component to provide an in-depth exploration to complement the quantitative data and aid the interpretation of trial findings.[89]

The principal research questions for the qualitative exploration were:

1. What are clinician's perspectives of urodynamics in the investigation of refractory OAB and how does this influence decision-making?
2. What are the experiences of participants leading to their decision to pursue treatment and what are their perspectives on investigations, potential treatment options and outcomes?
3. What are the reflections of patient participants following their investigations and treatment?

Methodology

Participants and recruitment

Clinicians

Clinicians from the FUTURE recruitment sites received e-mail invitations and a PIL outlining the purpose and aim of the qualitative study (see www.fundingawards.nihr.ac.uk/award/15/150/05). Those willing to participate provided written or electronically signed consent (see www.fundingawards.nihr.ac.uk/award/15/150/05) and semistructured interviews were conducted either at the start of the trial or within 6 to 12 months of recruitment starting.

Patients

Participants from the FUTURE trial who had consented to take part in the qualitative study were purposively sampled to promote diversity within the population.

A dedicated qualitative study PIL was provided and, following written, digital or verbal consent, a telephone interview was scheduled at the participants' convenience. Participant recruitment and interviews were conducted with the aim of achieving data saturation, the point at which there are no new emerging themes.[90]

Data collection

A uniform approach to interviews in all participant groups was incorporated, tailoring the focus of the interviews according to the group. The semistructured interview guide was designed based on the study aim, discussion between study researchers and review of the literature.[91] All the interviews were conducted remotely via telephone in line with the social distancing rules in place during the time of the study and were audio-recorded.

Data analysis

Interview recordings were transcribed verbatim and uploaded onto the QSR Nvivo 10 (QSR International, Warrington, UK) software package to facilitate data analysis using a thematic analysis process: familiarisation of the data collected, initial coding followed by generation and re-examination of themes.[92–94]

Qualitative study participants

The study comprised three groups of participants as detailed in *Table 23*.

TABLE 23 Characteristics of the three qualitative participant groups in the FUTURE study

Study		Number of participants	Age range
Pre-randomisation interview		27	24–79
Post-randomisation interview	Urodynamics arm	11	24–81
	CCA only arm	2	63–64
Clinicians		10	(No age demographics)

Study 1: clinicians' perception of urodynamics and its influence on decision-making

Aim

To evaluate the attitudes of surgeons on the influence of urodynamics on decision-making (at the start of the trial or 6–12 months after starting recruitment at their site). The interview primarily involved questions to understand clinicians' perception of urodynamics and its role in their patient's treatment pathway (see www.fundingawards.nihr.ac.uk/award/15/150/05).

Themes

A summary of the themes observed during study 1 (clinicians' perception of urodynamics and its influence on decision-making) is shown in *Table 24*. Also see *Appendix 5* for additional interview findings.

Conventional or current care pathway

Investigation offered

In line with NICE guidelines[3] the majority of clinicians confirmed that until they started the FUTURE trial it was standard practice in their hospital for patients to receive urodynamics if their conservative treatment, such as lifestyle changes, bladder training and medications, had failed to produce the desired results. Additionally, clinician responses revealed that urodynamics was used as a standard investigation procedure before subjecting patients to invasive treatment such as BoNT-A or sacral nerve stimulation (SNS).

> *Usually if they've been seen and tried on medication and failed and still have symptoms then conventionally, they'll just get urodynamics.*
>
> *04*

TABLE 24 Emergent themes from qualitative study 1

Clinician perception	Themes	Sub-themes
	Conventional or current care pathway	Investigation offered
		Treatment offered
	Factors influencing clinicians' decision and treatment allotment	Investigation information
		Guidelines
		Treatment availability
		Influence of patient characteristics
	Clinicians' observation of patient experience of urodynamics	
	Future practice	CCA – avoiding urodynamics investigation
		Do we need urodynamics?

UDS, urodynamics; CCA, Comprehesive clinical assessment.

For refractory overactive bladder we currently obviously do urodynamics before invasive treatments and when I say invasive that's Botox and SNS.

01

Treatments offered

Botulinum toxin injection A as first-line treatment

Most clinicians mentioned recommending BoNT-A as the first treatment to patients when conservative treatment had failed. This was because BoNT-A was perceived as a simple procedure that would either succeed or fail and would not have any long-lasting effects for the patient once it had worn off. Additionally, various other factors including local availability of the treatment influenced the clinicians' choice of treatment.

We would then go on to perform urodynamics, with a view to considering Botox injection as our next line of treatment.

10

Usually, Botox would be the first line of treatment […]. Botox tends to be a lot more black and white, that it's either going to work or it's not so it's a lot easier to know fairly quickly.

04

Other treatment options

Some clinicians stated that they offered other treatments such as PTNS or SNS along with BoNT-A. In some cases, however, these choices were influenced by patient-centric factors such as their history, or preference. It was also influenced by treatment availability or guided by investigation results.

I know that the NICE guidelines tell you to offer Botox first and we do that but also I feel that patient choice is important, so I do offer them, I tell them about the other treatment options.

01

Factors influencing clinicians' decision and treatment recommendations

Investigation information

Bladder diary

A bladder diary was revealed as one of the key instruments that facilitated clinicians with their decision-making, diagnosis and treatment assignment.

A well completed bladder diary, is by far the best guide really.

01

However, they acknowledge that the quality of the bladder diary varies among patients, thus resulting in a varying degree of reliability. As a result, some suggested that they felt urodynamics would give a better picture in addition to the bladder diary.

I think it depends on the patient to be honest with you, it always depends on the patient yes and how accurate is the bladder diary.

02

Early history and test reports

In addition to information gathered from the patient's bladder diary, clinicians emphasised the importance of patient history and test reports in guiding their decisions.

Well, patient history and bladder diaries are usually the two things that I look at basically.

04

I mean some of them come straight and say I leak only when I cough and sneeze. Others leak for example and then on detailed history you would find that it's urge incontinence rather than stress incontinence. So, history examination is good in guiding that there is nothing else.

07

Urodynamics

While clinicians expressed their reliance on the bladder diary and early test reports in deciding what treatment to recommend, some explicitly said that urodynamics provided some of the most useful information that strongly influenced their decision. Furthermore, some stated that urodynamics served as a confirmatory investigation and provided them with confidence to proceed with their treatment recommendation. On the other hand, there were clinicians whose responses revealed that the results generated through urodynamics did not influence their choice of treatment.

We usually proceed with urodynamics, just to be accurate.

07

I suppose it's confirmatory, that you are doing it to try and confirm what you think is going on and probably as much to rule out other things.

04

Even though the urodynamics might not have shown any overactivity then it wouldn't stop me from following the patients symptoms and offering them something like Botox. It's informative but it's not a deal breaker for me.

03

A clinician associated one of the key benefits of urodynamics with the quality time it gave them with their patient, adequate time to communicate and imbibe the patients' problems in depth.

It gives you an hour with the patient, I think that gives you the opportunity to talk things through in much more detail.

03

It also helps you establish rapport with the patient that you might be meeting for many years to come.

03

It gives you a much better feel for the patient, so I think it gives you an additional level of empathy for them for sure.

03

Guidelines

Existing guidelines such as NICE[95] strongly influenced clinician's choice of treatment pathway for their patients. There were, however, a few clinicians whose responses revealed that their decisions were not completely driven by guidelines; instead they prioritised patient preference.

We follow the guidelines so if it affects your overactive bladder then we do urodynamics.

02

I give them the option of PTNS, SNS and Botox and I know that the NICE guidelines tell you to offer Botox first and we do that but also I feel that patient choice is important.

01

Although the NICE guidelines states that we should always offer people Botox injections first, once we mention the requirement for self-catheterisation many people refuse to accept opting for Botox injection. Therefore, it is quite common for us to put the SNS and PTNS down as the other options.

08

Treatment availability

Another factor that influenced treatment recommendation was the local availability of the respective treatment. This was also tied to abiding with patient preference, as clinicians revealed that patient's willingness to travel to different locations to receive a treatment also influenced their ultimate treatment pathway.

> *I think we offer more SNS because we have it locally.*
>
> *01*

> *Well, we are not able to offer sacral nerve modulation here any more so we offer the sacral neuromodulation to go to [City D], or they're offered Botox injections.*
>
> *10*

Influence of patient characteristics

Patient characteristics and medical history

Clinicians acknowledged that a blanket approach to treatment pathway may not be suitable, as each patient may have unique clinical characteristics that may influence their treatment and outcome.

> *I think it's not one size fits all, I believe in tailor made management, guidelines are guidelines, quite often we see people who have scenarios which deviates from the normal pathway, it's always tailor made, I can't really say one test is superior to the other.*
>
> *08*

Additionally, clinicians expressed consideration of the patient's age, ability to self-catheterise or other concomitant health conditions that may potentially influence their treatment experience or outcome.

> *Patients with lack of ability to self-catheterise, again we consider they are a better candidate for nerve stimulation.*
>
> *05*

> *If I think they're not going to be able to self-catheterise then I will direct them away from Botox.*
>
> *01*

Patient preference

There were clinicians who stated that despite the NICE guidelines, patient preference would influence their decision and treatment. They identified abiding with patient preference was key to treatment satisfaction.

> *I feel that patient choice is important, so I do tell them about the other treatment options.*
>
> *01*

> *We offer the option to the patient and the patient chooses for herself.*
>
> *02*

Clinicians' observation of patient experience of urodynamics

From the clinicians' years of experience and witnessing their patients undergo urodynamics, they reported that their patients may be anxious when they come to have urodynamics, perhaps even describing fear, due to the invasive nature of the investigation and the use of catheters.

> *I think most are anxious because they're not quite sure exactly what it's going to be like.*
>
> *04*

> *Most of them are scared so they are expecting the worst.*
>
> *05*

Not many people in general like urodynamics, patient-wise. When I say 'don't like it', it's the apprehension, what is this test, its invasive catheters, tubes, things like this.

07

However, after having urodynamics many clinicians found that patients felt it had not been as bad as they had expected.

The majority of the people, actually we hear this from patients a lot, 'oh it's not that bad, not as bad as I expected'.

08

On the whole they find it's not as bad as they thought.

09

Future practice

Comprehensive clinical assessment – avoiding urodynamic investigation

Several advantages were described for CCA, with some clinicians reporting that undertaking clinical assessment without urodynamics increased the efficiency and speed of the pathway, avoided the risk of a UTI associated with urodynamics, and saved the patient from the stress and embarrassment of the urodynamics investigation, particularly related to the use of a rectal catheter. Cost reductions were also identified.

It makes the pathway quicker, it avoids the risk of UTI from urodynamics, and it saves money, no need for the machine, no need for the time, the personnel.

01

For the patient I don't think there is any other advantage apart from the stress of the test [Urodynamics] … so there are health advantages by avoiding the risks related to the test.

02

Some patients don't like the idea of a catheter especially a rectal catheter.

10

Do we need urodynamics?

Some clinicians did not like the idea of urodynamics being eliminated from the patient's investigation pathway altogether; instead, they suggested relying on urodynamics on a case-by-case basis.

With the current knowledge I would say keep the urodynamics after failed conservative treatment.

05

I suppose we can then say well ok for cases who do not respond to temporary stimulation then you can do urodynamics at that stage, rather than everybody.

01

Contrarily, some clinicians were open to discontinuing the urodynamic investigation as they felt it did not yield any added benefits to the care pathway and only viewed it as an inconvenience or hurdle.

My impression is that the results are going to be exactly the same in that I can't see that there's any advantage to having had urodynamics … it's not going to make any difference to the outcome whether they've had it or not.

03

As long as you do the diary and the bladder scan and a good history there's not a lot of advantage doing urodynamics.

10

Discussion

Among the clinicians participating in FUTURE, assigning patients to undergo urodynamics was the most conventional investigation practice followed. This was primarily as a result of abiding by NICE guidelines.[95] However, despite its widespread use, clinicians' perception of the usefulness of urodynamics as an investigation tool and perception of its benefits varied widely.

Most of the clinician responses revealed that bladder diary and patient history were viewed as key instruments that aided clinicians in understanding patient symptoms and assigning them appropriate treatment. Some, however, acknowledged the limitations of these instruments, highlighting the varying degree of quality obtained from the bladder diary. They stated that this is where urodynamics plays a crucial role. Despite its limitations, urodynamics was highlighted by clinicians as an investigation procedure that enabled them to confirm patient symptoms and provide them with the confidence to assign specific treatments to their patient. In addition, our study identified other factors which influenced clinicians' decision and treatment recommendations; these include clinical guidelines, local availability of treatment and patient preference.

The most recommended treatment was BoNT-A. The relatively simple nature of the procedure was a factor in its popularity. There were also some clinicians who recommended treatment options alternative to BoNT-A, such as PTNS or SNS, and relied on patient characteristics and preference such as their ability to self-catheterise.

The role of urodynamics in this pathway received varying views among clinicians. Some demonstrated high reliance on this investigation due to the additional information it generated, the confirmation it provided, and the additional patient–practitioner communication it enabled. Based on these benefits, some clinicians did not comply with the idea of urodynamics being removed from the care pathway. Instead, they recommended that the use of urodynamics may be limited to patients who absolutely require it. Contrary to these views, other clinicians were happy with the idea of not including urodynamics in their care pathway as they did not identify any beneficial contribution of urodynamics and mostly viewed it as a stage delaying patient treatment, increasing use of healthcare resources, and causing inconvenience to patients. They also expressed their observation of patient experience of urodynamics, with the majority describing patient anxiety associated with the procedure. However, they also stated that despite patients being apprehensive of the procedure, their post-investigation experience revealed that the procedure was manageable and better than their initial expectations.

Study 2: participants' experience and attitudes pre randomisation

Aims

1. To explore FUTURE trial participant experiences of symptoms and their impact prior to randomisation.
2. To explore participant attitudes to potential treatment options, invasive testing, and outcomes.

Themes

A summary of the themes emerging from study 2 (participants' experience and attitudes pre-randomisation) is shown in *Table 25*. Also see *Appendix 5* for additional interview findings.

Early symptoms and their impact

Symptoms

Many patients stated that they had been experiencing bladder symptoms such as urgency and leakage for several years.

> *I put up with it I suppose the last 5–6 years I suppose.*
>
> *P33*

> *My eldest child is coming up 7 … the issue started from when I had him and that was in 2015.*
>
> *P32*

They stated that the severity of their symptoms varied and experienced some good days and some problematic days. Many also highlighted that their symptoms had worsened over the years either with age, pregnancy or childbirth.

> *I've had bladder problems for many, many years and I've had times when it's been alright and then other times when it's become quite a problem. So, I get very uncomfortable.*
>
> *P09*

> *So that got worse with age and it got worse after I had my daughter so 6 years, 7 years ago now.*
>
> *P13*

Impact

Patients' experiences with bladder symptoms revealed that it had severely impacted their life and had an influence on their day-to-day activities.

Day-to-day activities

Many individuals shared occurrences of accidental leakage and embarrassing instances caused by their bladder problems. They expressed how it had restricted their participation in social events and physical and leisure activities. Their lack of involvement was also driven by the excessive planning required to manage bladder problems. This included ensuring proximity of toilets during a day out, packing extra clothes and pads, and planning journey breaks.

> *So, it is a bit restrictive, and I can't go swimming because I have to wear a pad because I don't want to be leaking in the swimming pool. So, things like that it does affect you.*
>
> *P19*

TABLE 25 Emergent themes from qualitative study 2

Pre randomisation	Themes	Sub-themes
	Early symptoms and its impact	Symptoms
		Impact
	Prior treatment, outcome and impact	Treatment options and its outcome
		Influence of early treatment outcome on future treatment
	Factors influencing patients' perception and choice of treatment	Treatment options – perception
		Treatment options – choice
	Expectations of treatment and outcome	Normality
		Increased bladder control
		Engaging in activities of preference
		Reduced anxiety
		Improved sleep
	Early perceptions of investigation arm – urodynamics or CCA	Positive perceptions
		Negative perceptions
	Treatment perception – initial perception of BoNT-A	Positive perceptions
		Negative perceptions
		Concerns of treatment failure

> *When you go anywhere you've got to look round and find a toilet before you can go do whatever you wanted to do. I don't go in town anymore because what if I didn't get a bus in time. It's just worrying all the time, you can't go for a walk, can't take the dog for a walk. It just stops you doing everything.*
>
> *P20*

It was also noted from the interviews that the bladder problems significantly impacted other key factors of an individual's life such as sleep, diet, work and relationships.

Sleep

An urge to urinate several times at night was common among most patients, with many reporting waking two to three times during the night. These individuals considered this one of the worst impacts of bladder problems and expressed how it was taking a toll on their sleep cycle and ultimately affecting their activities during the day.

> *Yes, it does, I'm up and down, up and down and I'm one of these that can't sleep once I'm awake so if it's 2 o'clock in the morning I'm wide awake then, then I'm absolutely shattered the next day.*
>
> *P03*

> *When your sleep's broken two or three times during the night … it does make you feel a bit groggy sometimes in the morning.*
>
> *P19*

Meanwhile, a participant also mentioned that the symptoms were more severe during the night compared to the daytime.

> *The night-time is the issue at the moment really … when I'm out I never really get to that desperate stage because I'm aware of where I am often where the toilets are, anyway but at night because I am getting I think personally run down, I'm very tired and a bit wimpy.*
>
> *P25*

Furthermore, some patients mentioned that they had avoided drinking more fluids before bed in order to avoid multiple trips to the toilet during the night, therefore highlighting the impact of their symptoms on their diet or fluid consumption.

> *I try not to drink before I go to bed.*
>
> *P07*

> *At night if I don't drink a lot before I go to bed I'm fine, I can sleep all night.*
>
> *P26*

Fluid intake

Patient experiences revealed that their symptoms and urge to urinate had affected their fluid intake, that is, they had either reduced or avoided drinking water or their favourite beverage. Irrespective of knowing the harmful impact of drinking less water, these individuals expressed that they minimised their water intake in order to avoid any potential accidents, leakage and sudden urgency of urination at unexpected times.

> *I think it varies on what I drink as well. I have cut down on my tea, fizzy drinks, any alcohol, I wasn't a big alcohol drinker anyway.*
>
> *P19*

> *But I try not to drink as much when I'm out and that in itself is not good either. I feel like if I have a drink I'm going to want to go to the toilet.*
>
> *P15*

Work

Bladder symptoms had a negative influence on most of the individuals work, due to their frequent need to use the toilet. Moreover, the severity of the symptoms prevented some from taking up a full-time job.

> *Well actually part of the reason I'm not working is this because I couldn't work, like I mean I'd spend half my day in the toilet, you know.*
>
> *P08*

> *I work part time from home because of everything that's been going on yes.*
>
> *P11*

In addition to these issues, some expressed the challenges associated with keeping their bladder problem a secret and mentioned they were in constant fear of being in an embarrassing accident or of being questioned about their frequent toilet visits.

> *I don't wear jeans unless they're black because I feel like, especially if I'm wearing blue jeans if I had an accident, you could tell and that would be even more embarrassing.*
>
> *P15*

> *Every work that I've had I've like, no you seem to be going to the toilet a lot, and … it's affecting life all in all.*
>
> *P18*

Contrarily, some participants revealed having little or no trouble at work and indicated to have managed their symptoms well. This lack of issues was mainly due to the individual's job type or post at work.

> *I suppose so because you see I only work in the afternoons and it's certainly not an issue at work.*
>
> *P27*

> *It wasn't too bad, because I worked in an office so I was sat down most of the time so it didn't really have a lot of impact, I could go to the toilet when needed.*
>
> *P19*

Relationships

Some patient responses revealed that the symptoms associated with OAB had impacted various relationships, including marital relationships, relationship with potential sexual partners, and friends.

> *It impacted on my marriage because I was constantly in and out of bed all night and my husband wasn't able to sleep, I started to wet myself occasionally.*
>
> *P30*

> *If I've met somebody it puts me off even wanting to sleep with anybody, to be in the same bed with somebody because sometimes I wake up in the night and there's a wet patch on the bed.*
>
> *P15*

> *My friends were getting so mad at me because we didn't do half of the stuff that we wanted to do in the time that we were there because it affected me really, really badly.*
>
> *P18*

Impact on mental health

The restrictions and planning requirements imposed due to the individual's bladder problems have instilled what participants described as 'a sense of panic' which has reportedly impacted their mental health. Patients also stated being in a state of constant fear of potential accidents, increased stress due to excessive planning prior to events, and a growing sense of isolation, loneliness and deterioration of confidence.

I think it impacted on my mental health as well because I constantly thought about it so as I'm constantly thinking about it, I'm constantly wanting to go to the toilet.

P30

And I felt very down and kind of depressed thinking gosh, at the time I was only 32 so then I realised that it's really bad.

P12

If we were going anywhere, I'd get this anxiety because I needed to know where the toilets was and that I could access them. It just actually controls all your everyday life.

P34

On the other hand, some stated that the symptoms got worse due to their stress and anxiety.

So, it is like a vicious cycle to be honest because obviously you get quite anxious about doing these things and it [bladder symptoms] gets worse, so you get more anxious and then it [bladder symptoms] gets worse.

P11

It gets to a point where I'm really stressed and I get very, very stressed so I just have to go.

P13

Prior treatment, outcome and impact

Treatment options and its outcomes

All participants had tried one or more treatments, including medication, physiotherapy and surgery. Individual experiences and satisfaction with medications and tablets varied. Some stated that the medication initially had a positive impact, but its effect wore off with time, while others stated that the tablets or side effects worsened their symptoms. Patients' experiences with physiotherapy and surgeries were similar – none of them were satisfied with the treatment outcomes and continued to suffer with bladder difficulties.

They gave me the tablets, some of them helped for a short while and then it just seemed to wear off. The second lot of tablets that I had they were really, really bad, if anything I thought they were making me worse than what I was.

P18

I had physio, an amazing lady … and then at some point, she said to me I can't help you any more I've done everything that I could.

P12

Influence of early treatment outcome on future treatment

Participants expressed dissatisfaction regarding their current treatment results (prior to joining the trial) and were unhappy with its overall outcome. Their experiences reveal that they had tried various treatment options and had perhaps run out of medications to try or were reluctant to continue experimenting with new medications due to potential side effects, need for long-term consumption or minimal effectiveness. This has therefore resulted in their seeking further treatment and enrolling in FUTURE in the hope of finding an ultimate solution to their ongoing bladder problem.

I have, I've tried medication and things which haven't worked so they stopped them. And really to me this is like the last option.

P05

So, it's got to a point now where I'm just trying to see if there's anything else I can either do to help myself or someone else can help me.

P25

Factors influencing participants' perception and choice of treatment

Treatment options – perception

Most participants were willing to try any treatment that was offered to them. This response was mainly triggered as they had reached a tolerance threshold and could not manage their bladder symptoms. Many were hoping to receive a treatment that would enable them to live a normal and stress-free life.

> *I'd be happy, no matter what I have to go through because like I said it's such a bane in my life.*
>
> *P18*

> *I want a solution and keep thinking I'll try anything not to be like this and to just get a good night's sleep.*
>
> *P03*

> *I wouldn't care, I'd try anything as long as I thought I was getting somewhere.*
>
> *P04*

Although most of the participants were open to any available treatment options, some had *certain preferences. For instance, a few expressed their wish to avoid surgical options.*

> *I would be very reluctant to have to go in for another very invasive operation. Like the ones that I've had, especially as they haven't worked.*
>
> *P17*

> *I don't know, I don't want any kind of surgery where you have to cut through and then do something complicated … just something simple that will resolve the issue. I don't like surgery.*
>
> *P26*

Some patients expressed relying on the information given by the medical team to guide their treatment pathway and, therefore, reported having done minimal research on their own, resulting in their lack of awareness of various potential treatment options.

> *I sometimes think it's better to not do that [own research] and just take the information you're giving me, and my nurse is giving me.*
>
> *P22*

> *They gave me leaflets and I read all the leaflets so there's no point sitting researching things online when I know the basics, you know what I mean.*
>
> *P07*

Treatment options – choice

Some participants highlighted various factors that could influence their choice of treatment and impact their willingness to accept the recommended treatment. The most mentioned factors included the following.

Travelling

While some participants demonstrated reluctance to travel far distances due to lack of their own transport, or inability to travel long distances while managing their existing health issues, others were willing to travel and did not identify it as a barrier.

> *So, if I had to travel somewhere for the day … that would be fine if it meant that I got better treatment.*
>
> *P15*

Yes, the location, if it's too far I wouldn't do it because as I say if I get out the car, I've got to go to the toilet so if I'm stuck anywhere that would be it, it would have to be local.

P21

The one that would bother me is getting to somewhere that's a distance away because I can't drive any more, and the transportation would be the issue. That would be my only problem.

P08

Time frame

There were mixed views among participants regarding their willingness to wait to receive a treatment. While a few were not concerned with the long waiting times, a few displayed worries, stating long waiting time may impact their day-to-day schedule. Some were also reluctant to undergo procedures that would require multiple hospital visits or involve a long recovery period.

I don't think I would have too long a wait. I've had this condition as I said over 20 years … so waiting a little while longer is neither here nor there really.

P22

But obviously I've got to factor all this in with working full time, you know so for me, I need something that's not going to drag on for months and months and months either.

P15

Side effects or impact on existing treatment or health issues

Some participants expressed displeasure at the prospect of proceeding with a treatment that would lead to severe side effects for fear of negatively impacting their existing health conditions and medications. A willingness to compromise and accept minimal side effects was described if the benefits outweigh the negative effects.

I'm willing to put up with some side effects as long as they're not too severe, I think there's a risk with everything isn't there so you've just got to, you'd be saying no to everything wouldn't you, if you looked at it that way.

P19

Something temporary that's ok. But not a side effect that will change my life completely.

P26

Expectations of treatment outcome

While exploring participants' expectations from future treatment, a few common goals were noted. These included the following.

Normality

Participants emphasised the desire to live a normal life. The meaning of a normal life varied for everyone, but in general it reflected the life they had before their bladder symptoms were aggravated.

Just being normal, I'm not looking for something out of this world it's just that you're normal again and you can do things, go out and not worry about where's the next toilet.

P03

I'm hoping that every bad symptom I have is gone, as obvious as that sounds.

P11

I would be hoping that this would stop, and I'd have a normal life like before.

P04

Increased bladder control

One of the common expectations of treatment outcome among the participants was to have more control over their bladder. Many hoped that the treatment would reduce the number of toilet visits. They expressed their desire to stop leaking and hence stop wearing pads.

> *Ideally I'd like to have some more control over my bladder.*
>
> *P24*

> *Well, I would like the leakage to stop, that would be amazing.*
>
> *P13*

> *To stop wearing pads for a start, and hopefully I can get some more control over my bladder so that when I want to go, I've got time to go and not have that urgency to get there quickly.*
>
> *P19*

> *I'm hoping to be able to go out without having to consider a toilet at all times.*
>
> *P16*

Engaging in activities of preference

Participants hoped to restart socialising and taking part in activities of their liking such as going for a run, keeping physically fit, and travelling.

> *I mean it would be amazing if I can do basic stuff with my kids, if I can just go to the park, if I can even run after.*
>
> *P12*

> *I want to be able to go on a night out without constantly thinking oh my God is there going to be a queue in the toilets and stuff and being able to hold it in at least a couple of minutes instead of it like flooding out.*
>
> *P15*

> *I'd go out a bit more and enjoy my life a bit more because at the moment I'm not enjoying anything really.*
>
> *P21*

Reduced anxiety

Participants further voiced their wish to minimise worrying and stop being in a state of constant stress caused by thinking about how to manage their bladder symptoms.

> *Well, the most satisfactory outcome would be that this would all stop and that I could just get on with my life without this being a constant anxiety.*
>
> *P09*

> *I think that's what I'm hoping for so I'm not anxious every time I go out anywhere, even on a drive. Going any distance.*
>
> *P23*

Improved sleep

Getting a good night's sleep was another commonly hoped-for outcome. Since nocturia was one of the main symptoms of the participant's bladder problem, resolving this was one of their key goals. They expressed how better sleep could improve their quality of life and bring the 'normality' factor back.

> *To go to bed at night and once I'm in my bed to sleep all night, get up the next morning, how it used to be, need the toilet and that would be it. Feel normal again I suppose.*
>
> *P02*

Getting a decent night's sleep, I'm very sleep decremented at the moment because I just can't, as soon as I move, I'm finding that my water's coming away.

P05

Managing expectations

Although participants had various expectations, they seemed to demonstrate a level of understanding that all their hopes for their post-treatment life may not be met. They, therefore, expressed that they would be satisfied even if they received minimal relief from their current bladder problems and their symptoms became more manageable post investigations and treatment.

To be honest with you I don't expect being 100%.

P03

70% that's fine. I'm not hoping 100% as if you don't leak at all or something. I don't mind a little bit of leaking here and there but not like what I'm having now.

P10

Early perception of investigation arm – urodynamics or comprehensive clinical assessment only

Participants had mixed perceptions and reactions towards receiving urodynamics or being assigned to the CCA only arm. There were participants keen to undergo urodynamics in hope of finding a solution, or because all other treatments had failed, and they therefore felt more hopeful and validated to have a choice or an investigation option still available. On the other hand, a similar proportion of participants were put off by the thought of urodynamics either because of the invasiveness of the procedure or due to the perception that the procedure would only delay their treatment. Among those who were not keen to undergo urodynamics, some were willing to put up with it if it meant finding a solution to their bladder problems.

There were a few participants who had a previous invasive urodynamics experience and were more confident to undergo the investigation. However, there were some with previous urodynamics experience who were unhappy with the procedure or considered it pointless to repeat it.

Positive perceptions

Keen or happy to undergo urodynamics

I'm actually not bothered about it to be honest. If me taking part in the study means that they can try and get to the bottom of what's going on with me and it does help other people going forwards.

P15

This makes sense[having urodynamics] rather than to be dished out some treatment and then do it and then it might not be right and so give out some more treatment.

P18

More prepared due to previous urodynamics experience:

That was what I had in 2015 it established I had an overactive bladder … I don't actually have a problem with procedures at all.

P25

Well, I've had no bad recollections of it. I mean I had it done and that's it, it's only a bit embarrassing when you sort of think you're weeing yourself, that's it.

P20

Negative perceptions

Unhappy with the idea of urodynamics:

Obviously I'd rather not have it …. So, my reason is because I do get quite nervous …. So, I'd rather not have it because I don't want to be in pain. I don't want to be uncomfortable.

P11

I hope I don't have to have it; I'm dreading it.

P14

Unhappy but open to undergoing urodynamics:

Well, I don't really know, it's hard because I'm not really fancying catheters but if it has to be, it has to be.

P02

If I have to have urodynamics I have to have them, I mean I'd prefer not to but if I have to, I'll just do it. As long as it gets things moving, I will just go with the flow really.

Unhappy with previous urodynamics experience and hence not looking forward to another:

To be quite honest with you I've already had the dynamics test, which to have to go back through that again would seem silly because of us already having it done and you already sort of know what the outcomes have been of that.

P05

I've had the urodynamics twice before, they're not something to relish.

P22

Treatment perceptions – initial perception of botulinum toxin injection-A

While discussing treatment options, all participants in this study discussed BoNT-A as their potential future treatment; therefore, BoNT-A and its perception has emerged as one of the key themes in this study.

Positive perceptions

Some patients were happy to undergo BoNT-A as they identified it as a quick procedure and were willing to try it in the hope it improved their symptoms.

I'm quite happy to go ahead with the Botox treatment, it seems as if it's a fairly easy procedure. I'm quite happy to go along with that.

P22

Well, it's brilliant that it's a 5-minute procedure, I'm really happy that it's so quick. I'm happy that I'll be awake because I'm terrified of general anaesthetics.

P11

Negative perceptions

A few individuals were apprehensive of the procedure due to its invasive nature. They expressed their fear and some highlighted that although they would undergo the treatment, if recommended, it was not something they were looking forward to.

Terrified but I think it's got to be given a go.

P14

I was offered this Botox treatment, which I was a bit wary of to start with because they said that about 15% could go wrong, out of 100 and that would involve me putting a catheter in myself which I was a bit unsure of what to do with that.

P19

> *I'm very anxious about that [Botox] as well because I can't imagine what that's going to be like.*
>
> *P01*

Concerns of treatment failure

Quite a few patients were nervous due to potential failure of the treatment or were worried that the BoNT-A procedure would hinder their urination and ultimately force them to self-*catheterise*.

> *I'm worried that I will be this unlucky person because I could end up with an infection and obviously I have to do it [catheterise] myself which is scary as well. But I think this is one of the risks*
>
> *P12*

> *I know you might have problem then passing urine and things, you might not, but you might. But that is a bit of a worry obviously because I don't really want to have more problem.*
>
> *P13*

Discussion

Participant experiences reveal they have put up with their bladder problems and associated symptoms for many years. Information extracted through the interviews provides clear indication of the negative impact that bladder symptoms have on their day-to-day lives. It has caused severe restrictions on their activities and has ultimately taken a toll on their mental health. Additionally, failure or poor efficacy of past treatments has added to their existing disappointment and frustration. This scenario, therefore, has driven these individuals to seek further treatment.

Although the majority of the participants were keen to undergo further investigations and seek treatment for a cure, some revealed several personal and external factors that potentially influence their perceptions of available investigation and treatment options. Similarly, their perceptions of urodynamics were influenced by a few factors, where positive perceptions were influenced by their strong drive to find a successful treatment, or confidence from previous invasive medical experience. On the other hand, negative perceptions were triggered by fear of the procedure or lack of confidence associated with the benefit of the procedure or negative experience with previous urodynamic procedures. A similar pattern was noted for participants' perception of BoNT-A as a treatment: while some were optimistic to undergo BoNT-A, there were some who were reluctant due to the invasiveness and stages involved with the procedure. Ultimately, however, every participant's goal was to get through their treatment pathway in order to achieve a successful outcome.

Furthermore, participants' eagerness to move forward in their treatment pathway was driven by several hopeful scenarios associated with post-treatment outcomes. The shared expectation among all participants was to get back to living a life without their bladder symptoms taking control of their choices and actions. However, their previous experiences of failed or ineffective treatments have resulted in their being more cautious of what they could expect as a result of their upcoming treatment.

Additionally, participant responses revealed their limited knowledge of various treatment options, as all participants in this study were aware of only BoNT-A as a therapy, thus highlighting the need for increasing patient knowledge and awareness of various treatment pathways in order to enable them to make a more informed choice.

Study 3: participants' experience of urodynamics and opinions regarding treatment outcome to include evaluation of treatment satisfaction or desire for further treatment (3–6 months post treatment)

Aims

1. To explore participants' perception of their randomised arm, their treatment experience and outcome.

2. To understand participants urodynamics experience and its potential impact on their treatment and outcome.

Themes

A summary of the themes emerging from study 3 (participants' experience of urodynamics and opinions regarding treatment outcome) are shown in *Table 26*. Also see *Appendix 5* for additional interview findings.

Urodynamics as an investigation pathway

Participants who had undergone either urodynamics or CCA only shared their views on being randomised to receive urodynamics or not, respectively. Based on their experiences and perceptions the following themes were derived.

Individuals who were randomised to undergo urodynamics displayed varying responses.

Perception of the urodynamics arm

Hopeful

Having to undergo an additional clinical investigation made some participants feel more validated. They expressed feeling more optimistic of finding a solution and nearing their goal of rectifying their bladder problems. Furthermore, for a few, this stage was deemed to be *hopeful as all their previous treatments or investigations had failed.*

> *But knowing that it's like an actual problem I'd be having tests for just makes me feel more validated.*
>
> *P11*

> *And I thought well this is going to help, if I do this it's going to help people further down the line hopefully, so that was my thinking.*
>
> *P34*

Nervous

There were participants apprehensive about undergoing urodynamics. This was mainly due to the invasiveness of the procedure or due to the fear of the unknown.

> *As I thought about the information, I'd been given I thought I don't really want to go ahead with the urodynamics.*
>
> *P09*

> *I was nervous because I was told pretty much what to expect at the urodynamics.*
>
> *P11*

TABLE 26 Themes emerging from qualitative study 3

Post randomisation	Themes	Sub-themes
	Urodynamics as an investigation pathway	Perception of the urodynamics arm
		Perception of the CCA arm
	Urodynamics experience and perception of usefulness	Experience
		Perception of usefulness
	BoTN-A early perception and experience	Awareness
		Procedure experience
		Perception of repetition
		Catheterisation
	Post-treatment outcome and impact	Patient satisfaction
		Treatment outcome
		Treatment impact

A bit nervous because it's something I hadn't had before, but It was fine.

P36

Unhappy

Some expressed complete displeasure about being randomised to receive urodynamics. This response was mainly due to the discomfort associated with the procedure. Furthermore, one participant declined urodynamics.

I didn't like it and I'm quite a private person, so it was a big thing for me to go through that. I didn't think it was very nice to be honest.

P29

I wasn't looking forward to it at all because I knew that it was obviously going to be a bit uncomfortable.

P11

I was actually really disappointed, and I actually cancelled my appointment for the urodynamics because of all the information I'd been given, I just felt that it wasn't really the way forward for me.

P09

Confident from previous invasive procedure or diagnosis

Most of those who had previously undergone urodynamics or an invasive diagnosis experience were more confident to undergo the procedure. Additionally, some demonstrated greater acceptance due to their experience with pregnancy and childbirth. Therefore, these individuals were not reluctant or unhappy, instead they were less bothered on being assigned to the urodynamics arm.

Before the urodynamics went ahead I had my bladder examined, you know so with the camera put up to make sure obviously to exclude anything going on so that, I suppose, helped prepare me for the urodynamics.

P35

It's quite invasive but having had children and had various operations no it didn't bother me at all.

P30

Open to any procedure to stop the problem

Many participants were willing to undergo urodynamics by putting aside their fears and discomfort, as they were keen to find a solution to their problem, and therefore had a positive outlook on being randomised to the urodynamics arm.

Usually, I just jump through the hoops they ask me to do to get things done. Each time I'm just hoping something will work, you know?

P31

I needed to find out why this is happening and if there was a way that it could be either minimised or stopped so having something like that done was just a help, I didn't find that a problem at all.

P30

My thoughts were positive because if the medication wasn't working, I was keen to try anything that might work or at least investigate what was going on, so I had no negative thoughts about it at all.

P35

Perception of the CCA only arm

Only two participants from the comprehensive clinical assessment only arm were interviewed due to issues within the trial design making it difficult to identify participants at the correct time point in the clinical treatment pathway. Perceptions of both these participants were different, with one expressing delight for having avoided urodynamics, mainly because she was relieved to have avoided a procedure which was deemed uncomfortable and invasive: 'Oh yes,

I was thrilled' (P08), whereas the other participant expressed unawareness regarding the urodynamics procedure, thus having no opinion either way.

Urodynamics experience and perception of usefulness

Experience

Embarrassing

Some participants considered the urodynamics procedure humiliating and were uncomfortable as the investigation required them to be quite exposed and urinate while being watched.

> *It's still demeaning, and I didn't like it.*
>
> *P29*

> *It wasn't at all a pleasant experience.*
>
> *P11*

Non-embarrassing

There were individuals who were not affected by it and did not consider the procedure difficult or demeaning.

> *No, no. you can't feel embarrassed because you're asking for treatment, so yeah, giving you treatment, what's the point in being embarrassed about?*
>
> *P28*

> *I did not feel any embarrassment at all, even when the fluid was pushed into my bladder, and I obviously couldn't hold it. So, which was what the test was all about.*
>
> *P35*

Painful and uncomfortable

There were participants who found the procedure to be painful and therefore categorised it as an awful experience to go through. Reports of physical discomfort or uneasiness felt due to the presence of the medical team around them were noted.

> *But my experience with it no, overall is it wasn't as if I'd like put myself forward to do it again. Just because of the pain, simply because of the pain.*
>
> *P11*

> *When they were sort of filling up my bladder, it then became very uncomfortable.*
>
> *P32*

> *There was about four people in the room, and I was very uncomfortable with it. And to me, you should maybe be left on your own.*
>
> *P28*

Reassuring

Undergoing urodynamics was deemed to be reassuring for some participants, as they felt some action was taken in order to resolve their problem. They considered the process beneficial and believed it yielded results that had potential to drive success of their future treatment.

> *Yes, I would, I would rather have had it definitely because it did actually show up that I still have interstitial cystitis and frequency and whatever so yes, I was glad to get it.*
>
> *P30*

I found it a very reassuring experience. The staff there, the consultant and a nurse …. The urodynamics actually confirmed what the problem was and therefore a course of treatment could then be planned.

P35

Perception of usefulness

Most of the participants regarded the urodynamics as a useful procedure. They believed it provided the medical team with information, hence enabling them to get a clear picture of their bladder problems and further aid in deciding the most suitable treatment. These individuals were also willing to repeat the procedure if required. However, a few were convinced that urodynamics did not make any valuable contribution to their treatment journey and considered it an unnecessary hurdle in their pathway to cure.

Positive perception

So, I kind of thought, well, at least it's showing them what I need doing and, you know, confirming what I need doing.

P31

Urodynamics actually confirmed what the problem was and therefore a course of treatment could then be planned. So yes, if I had to go back in time, no hesitation at all in going for the urodynamics.

P35

Negative perception

The negative perceptions were associated with a rather inconclusive urodynamics investigation.

So, I have done urodynamics, but I think it was fairly inconclusive.

P32

[The care team] couldn't make sure that was accurate because one of the connections of the pipe had come loose but I thought to myself I'm not going to have that again, I thought I personally wouldn't have that again.

P34

Botulinum toxin injection-A early perception and experience

All participants in this qualitative component of the FUTURE study received BoNT-A as their treatment. Therefore, BoNT-A and its experience have emerged as one of the key themes in this study.

Awareness

Many were familiar with the term BoNT-A, but they were extremely surprised after learning it was a treatment for their bladder problem since they identified it as something only used in the cosmetic industry. Some expressed having vague knowledge of this treatment for OAB as they knew someone who had the treatment or had heard it from the medical team at an early stage of their diagnosis or treatment pathway.

Unaware

I was quite surprised it was an option to be honest, I didn't think Botox worked for anything like that.

P29

I think I laughed because people normally get it on their faces. I had never ever heard of it and a lot of people I'd spoken to had never heard of it.

P33

Aware

I've known about Botox for a while.

P32

Well, I didn't really understand it, but I knew somebody that had had it for the same reason and that it had helped her.

P34

Procedure experience

Among the participants who had undergone urodynamics, most shared a positive BoNT-A experience. Some of these pleasant experiences could be attributed to the either the general or local anaesthetic the participants received. A few categorised BoNT-A as a better experience compared to urodynamics, whereas there were individuals who identified the procedure as fascinating as they were allowed to view the procedure on screen while they were undergoing it.

On the other hand, two of those who did not undergo urodynamics and some from the urodynamics arm described BoNT-A as a moderately painful and uncomfortable procedure. One stated that they were not well aware of the procedure, which resulted in their being less prepared for the treatment, and hence the discomfort. In addition to this, there were two individuals, one from each arm, who declined BoNT-A after learning the details of the procedure as they feared potential pain, infection or need to self-catheterise.

Urodynamics arm

I had anaesthetic, so I didn't feel anything.

P30

So I knew that it was going to be a catheter but they used some kind of anaesthetic, numbing thing and honestly I didn't expect it to work but it did, I actually didn't really feel much of the catheter going in …. So yes, it was as comfortable as it could be really.

P11

Quite fascinating. I watched it on the screen. It's not so painful or anything.

P33

It's very difficult, I mean you read about Botox and oh it's fantastic … it was intensely painful, it was really, and I'm not a wimp, it was really painful, and it did nothing.

P14

Comprehensive clinical assessment only arm

Well, it was a little uncomfortable at times, like to almost being painful, briefly, very briefly but yes I was glad when it was over.

P08

Perception of repetition

The potential need to repeat BoNT-A received mixed reaction among participants. None of the participants were looking forward to repeat BoNT-A. They were, nevertheless, willing to make a compromise and endure the procedure in return for greater control over their bladder. Some, however, displayed complete displeasure as their initial BoNT-A had failed to produce the desired result.

I thought I don't really want it. If there was something else, they could do that would be great, but if it stops me from keep piddling, as often as I do.

P31

I'd rather have the procedure than what I had before. Yeah, rather because I can go out. I can live a normal life now.

P35

Catheterisation

Initial thoughts

None of the participants were happy with the idea of self-catheterisation. However, many were open to do it if it was a requirement. Some expressed their concerns regarding the potential difficulties they would face if they had to self-catheterise. This included managing to self-catheterise if they considered themselves to be overweight, or fear of infection. Some deemed it an inconvenience if they had to continue doing it in the long term. Furthermore, one declined BoNT-A due to the potential need to self-catheterise.

> *Well, at first I said there's no way I can self-catheterise I am a big woman.*
>
> *P31*

> *I wouldn't mind for a short period of time, and because I work from home, it would be easier. If I was back in the workplace, or if I was, you know, out a lot of the time I think I would become quite self-conscious if I had to do it.*
>
> *P32*

> *I mean, it's just if I had to do it, it's an inconvenience, but it's a necessary inconvenience as far as I'm concerned.*
>
> *P35*

Experience

Inevitably several participants were required to self-catheterise following their BoNT-A treatment. There were positive and negative experiences of participants who had to self-catheterise. Positive experiences involved participants expressing their satisfaction with their being able to completely empty their bladder. Most of these individuals were willing to continue self-catheterisation for as long as required. Negative experiences that participants shared included pain, discomfort and numbness due to continual need to self-catheterise.

> *In the beginning it was quite uncomfortable, and I did get a nasty infection for which I had to have antibiotics but apart from that it's not caused me any issues …. It's a really weird sensation to be honest because my whole body feels empty whereas before it didn't …. So, it's absolutely amazing and it would not bother me if I had to catheterise for the rest of my life.*
>
> *P30*

> *I've been trying to self-catheterise and I am really struggling with that.*
>
> *P08*

Post-treatment outcome and impact

Patient satisfaction

Patients from the urodynamics arm and one from the CCA only arm expressed their pleasure following BoNT-A treatment. Some clearly described their satisfaction with the outcome and were thrilled to have more control over their bladder.

> *I'm OK. Yes, yes, I'm OK. The last time I was in seeing Doctor x, he was quite happy, and I was quite happy.*
>
> *P28*

> *Yes, very satisfied …. No. I mean I rather the whole thing hadn't happened, but it did. So no, I I'm entirely satisfied with the service that I got once I had been referred to the urology clinic. They were fantastic.*
>
> *P35*

Treatment outcome

Many patients shared positive stories of their treatment outcome. For some the positive impact was immediate, while some had to wait a few days to a week to spot differences and improvements in their symptoms.

Positive outcome

But to be honest great, really great. I felt, I was watching the urgency just in case it came on me, but it's been smashing.

P29

Absolutely brilliant because some days I can go 4–5 hours without having to go to the toilet, whereas before in that time I probably would have gone about 20 times.

P30

Those who were unhappy with the treatment outcome, that is the BoNT-A had failed, and their bladder symptoms continued to prevail, expressed tremendous disappointment as they were hoping and relying on this treatment to work.

Negative outcome

I'm sure I am leaking when I'm sat there, I am not really aware of it. you know?

P31

I was really hoping for the Botox to work, and it hasn't. I can probably run slightly longer but I still leak … it didn't help. It hasn't worked as well as I hoped.

P32

And they kept saying it takes 2–3 weeks to work oh it takes 3–4 weeks to work. And then they said we've never known anybody where it hasn't worked at all before. Well, I don't believe that. I can't be unique in that respect, and they just don't have any answers.

P14

Treatment impact

Day-to-day

Participants said they were able to go out and socialise more. They expressed their pleasure at being able to get back doing activities such as shopping, driving, travelling, working or even enjoying an extra drink without having to worry about their bladder. Some expressed extreme satisfaction and stated all their symptoms had disappeared and they were able to live a normal life like a healthy person. They were thrilled with the reduced frequency of their toilet visits. Additionally, the outcome seems to have reduced the burden on the participant's mental health, with them being more carefree and confident.

Yes, just like not having to think ahead all the time, where we'll be sitting, where we'll be going, who am I with, am I comfortable…. It's took that bit of pressure away.

P29

I have a few more fizzy drinks than I normally would which is like, it sounds silly to say because it's such a normal thing for people.

P11

I mean I could go with my friends … on day trips on the coach. I wouldn't be able to do that before.

P34

Yes, it's removed all the symptoms completely.

P36

Patients also mentioned spending less money on pads and stated they had either stopped or continued to wear pads only as a precautionary measure.

I am not spending so much money on the pants as I used to. I was spending a fortune before but now I've only got to get them for the night-time.

P33

I'm still using pads, but not as many. it's more a precautionary measure because I still leak from time to time. But not as much as I used to.

P28

Among the few who reported negative treatment outcomes, some stated that their treatment had made no difference to their condition, with one even mentioning that their symptoms got worse after the investigation and treatment.

No difference whatsoever …. Well initially for about 2 weeks I was going more, it was awful, it was exhausting …. It was really bad over a three-day period so in the end the nurses there fitted me with a catheter because I just couldn't do anything … they took the catheter out and it was just exactly as it had been before, couldn't go more than an hour and a half in the night, well was just a total prisoner to it, couldn't do anything.

P14

Sometimes I feel I got worse, you know? It's like a vicious cycle.

P31

Sleep

Some highlighted that their sleep had improved post treatment, to the point that their friends and family had noticed improvement. A few credited this improvement to self-catheterisation. One also noted that although their symptoms during the day had diminished, nocturia continued and hence they had a disturbed sleep even post treatment.

I sleep better, my friends tell me I don't look so haggard.

P30

I've had the odd night where I'm sleeping right through and getting up comfortably so that's good.

P29

I'm OK at night now yeah because I self-catheterise. When I go to bed most nights.

P28

Well, the thing is the only thing that hasn't really changed is not sleeping. I try to stay awake as long as possible but eventually I nod off. I am asleep for about 3–4 hours and then I'm awaken.

P33

Comprehensive clinical assessment only arm

Only two participants from the CCA only arm were interviewed. Experiences of their treatment pathway and outcomes differed, with minimal overlapping of emerging themes. Therefore, these experiences have been described in terms of case studies to articulate reflections on this course of investigation. Participants' experiences have been summarised to highlight distinctive stages in their treatment pathway comparable to the descriptive analysis provided for those who underwent urodynamic investigation.

Case study 1

The first participant was assigned to the CCA only arm and expressed being thrilled to have avoided urodynamics. A key reason for this response as stated by the participant was that keeping track of urine output or maintaining a bladder diary was a burden in itself and thus undergoing urodynamics would only add to this. This participant was assigned to receive BoNT-A and described the procedure as uncomfortable. However, the participant expressed satisfaction with the treatment outcome and stated that, although it took a while before their symptoms began to improve, the ultimate response to the treatment has been satisfactory. The participant further emphasised that, considering the positive outcome of BoNT-A, she was willing to repeat the procedure irrespective of the slight discomfort associated with it. A positive reflection of the investigation and treatment pathway was therefore articulated for this individual.

Case study 2

The second participant assigned to the CCA only arm demonstrated unawareness of the urodynamics procedure, thereby hindering the possibility of exploring their perception of not undergoing the urodynamic investigation. This participant was assigned to receive BoNT-A but was unhappy with the outcome and stated that the treatment had made no difference and did not result in any improvement of her bladder symptoms. This participant has, therefore, moved on to receive treatment outside the recommendations of the NHS and mentioned relying on acupuncture. She stated that this has resulted in some improvements and was in turn happy to continue in this pathway for as long as it enables her to manage her symptoms. A negative reflection of the investigation and treatment pathway was therefore articulated for this individual.

These cases highlight the different experiences of the two participants interviewed in the CCA only arm. While we are unable to draw conclusions from these individual accounts, they demonstrate the different experiences that women can encounter when undergoing similar investigation and treatment pathways.

Discussion

The perspectives of clinicians and participants in FUTURE have provided valuable insights into the investigation and treatment pathways for women with refractory OAB symptoms. In combination with the trial findings, these data can inform practice in this area informed by the accounts of the individuals involved in these encounters.

From a clinician perspective, we identified that urodynamics is commonly practised for women with these symptoms and used to inform treatment decision-making. The reason for including urodynamics is described as being multifactorial. The main reasons for its inclusion is to conform with NICE guidance, clinical judgement indicating it is warranted, and where there is a quest for additional information to explain symptom presentation.

The bladder diary and clinical history-taking were identified as key assessments for decision-making in this clinical population. Recognition of the impact of variable quality in the completion of diaries was highlighted, as accuracy is critical to its value.

Botulinum toxin injection A was described as the most common treatment choice, liked for the simplicity of its provision and general accessibility. It is viewed as a valuable first option to see if it will be effective and continue with other treatment considerations if unsuccessful. Variability is evident in the scope of other available treatments that are offered, largely due to service provision in the setting.

Preference for the use of urodynamics varied, with some describing it as an important component to the investigation of women with these symptoms and others felt it was not essential and a waste of resources and questioned its value in informing treatment pathways.

From the participant perspective, a clear story of enduring and impactful symptoms was described, caused by their urinary symptoms. These symptoms affected all participants to varying degrees in every facet of their daily lives and an exasperated desire to return to normality was articulated.

Decision-making was explored, prior to knowledge of the investigation or treatment that would ensue, highlighting that this is a complex area that has many influences that must be considered. Previous experience of investigation and treatment, potential side effects, time frames and geographical location are all important factors that influence a decision to be able to undertake the proposed clinical pathway. While many participants expressed the feeling that they would do whatever it takes to resolve their symptoms, these factors alongside personal circumstances are critical in ensuring patients are at the centre of the decision-making process.

More specifically, considering urodynamic investigation, an equal distribution of participants were willing to undergo urodynamics or were reluctant to undergo urodynamics. From our findings, it appears that those most likely to be willing to undergo urodynamics were those who perceived the investigation to be useful and value-adding in their treatment

pathway. Furthermore, confidence to undergo urodynamics was mostly noted among those who previously discussed their problem with peers or had previous experience of urodynamics, or an invasive investigation. Among those who were unhappy to undergo urodynamics, this response stemmed mainly due to their perception of the discomfort and pain associated with the procedure. Additionally, a few individuals were apprehensive of the urodynamics process. However, despite feeling nervous they were willing to go through the procedure with a positive outlook if it would better inform the treatment decision-making, because their previous treatments had failed, and they considered this pathway as their last resort to arrive at a treatment plan.

The two participants who were interviewed who underwent CCA only had differing accounts, with one pleased to not have urodynamics, having dreaded the procedure, and for the other a complete unawareness of urodynamics, making it difficult to explore her perception of this investigation. This highlights the need for clear information and guidance regarding the options to ensure patients are fully informed.

The experience of participants undergoing urodynamics varied. For some it aligned with their initial perceptions either negatively or positively. For others, there was an altered perception following the investigation, usually from a negative to positive perspective, with it often being described as 'not as bad as expected'. This suggests that counselling patients regarding the procedure and its expectations may help in improving the outcome and experience of the investigation.

Having had urodynamics, participants seemed more at ease with the BoNT-A procedure, except a small minority who voiced displeasure and found the treatment procedure uncomfortable. Irrespective of their initial perception and experience of BoNT-A, a few participants were concerned at the idea of having to repeat BoNT-A and carry out self-catheterisation for a prolonged period. Nevertheless, despite these worries, most of the participants noted that the benefits of the procedure outweighed the drawbacks and inconveniences associated with it.

A clear improvement of symptoms was described among the majority of the participants. Although the treatment failed to produce the desired outcome for a few, a considerable majority of participants stated that the treatment had a positive impact and had tremendously enhanced their quality of life.

Conclusions

It is clear from the results that both advising and undertaking a clinical investigation and treatment pathway for refractory OAB involves complex decision-making. Clinicians identify the necessity of clinical assessment/investigations for the effective treatment of women with these symptoms. The value of important tools such as bladder diaries, clinical history-taking and urodynamics is recognised. Patient participants have clearly articulated the desire to resolve bladder symptoms that impact their everyday lives. Opinions are mixed regarding the appetite for urodynamics, varying from those who are reluctant to undergo this investigation, to those who are prepared to undergo it if it serves a purpose in guiding treatment decision-making, and those who are happy to go along with whatever is advised. Understanding that this diversity exists provides an opportunity to appropriately counsel women regarding their investigation and treatment pathway choices.

Clarity regarding the indications and value of urodynamic investigation that are clearly articulated to women with refractory OAB is key. Understanding if and why urodynamics will add value to the treatment pathway would be a critical component to providing more comprehensive counselling to enable women to make informed choices. Empowering patients to understand their options and why certain pathways are advocated is necessary to ensure shared decision-making where possible and particularly applies to this area of clinical care, given the sensitive nature of urodynamics and the experiences articulated.

The rich data and descriptions provided by both clinicians and participants will inform patient counselling regarding this investigation and treatment pathway, as lived-experience accounts are extremely valuable.

Comparison with evidence base

Our findings confirm previous findings in this area related to women undergoing urodynamics, not only for investigation of OAB[96–98] Some studies have found that women report urodynamics to be uncomfortable or even painful, particularly during the insertion of the catheter into the bladder. However, other research has suggested that the level of discomfort varies widely among women, and some may not experience any discomfort at all.

Additionally, some women have reported feeling embarrassed or anxious during the test, particularly if it is their first time undergoing urodynamics. External influences include the type of catheter used, positioning during the test, skill of the clinicians, age, medical history and previous experiences of medical investigations. Crucially, counselling is vital and the voices of women with lived experience included in this report will be extremely valuable in fully informing women about their assessment/investigation to enable them to prepare appropriately.

Limitations

Our key limitation is that participants in the CCA only arm were substantially fewer than the urodynamics arm. Despite the smaller sample size, we were still able to obtain valuable insights from the interviews conducted with these two participants, which are presented in the form of case studies. While the limited number of participants in the CCA only arm may have some impact on the generalisability of our findings, we believe that the insights gained from these interviews are still valuable for informing potential future research and clinical practice.

Chapter 7 Urodynamics quality assurance

Introduction

To be assured of good quality measurements and accurate urodynamics data recording, a guide for standardising urodynamics best practice (see www.fundingawards.nihr.ac.uk/award/15/150/05) was developed in conformity with the ICS Good Urodynamics Practices.[69] This guide and process were deemed necessary, as concerns had been raised previously in the literature about the impact of the quality of urodynamic studies on the reliability of diagnostic results.[99] A 'think tank' had considered it was clear that technique affects the quality of a urodynamic test, and with other factors it will affect the utility and perceived value of that test.[99] One publication looked at data from two large male urodynamics trials and found that a significant proportion of sites did not undertake equipment calibration checks or had findings that were affected by artefacts in the signal.[100] A robust methodology for obtaining a measure of QA was therefore developed for the FUTURE trial to give an indication of how far this problem of quality might have affected the data collected.

The guiding principle was that the trial includes an appraisal of current urodynamic practices throughout the UK. The role of the QA process was not to force sites into compliance with a rigid protocol – which would be a kind of 'urodynamics police' – but to ensure that the data used for analysis were based on a reasonable level of assurance for its quality yet reflected the standard current clinical practice in the UK.

Methodology

A system was established to review urodynamic traces from all participating sites, to give assurance that the quality of the urodynamic technique and interpretation was up to standard for use in the trials data analysis.

Initially, the guide for urodynamic best practice was circulated to all sites and the details were explained during the initial trial meetings. An outline of the contents of the guide is given in *Table 27*.

The process of urodynamics QA in the trial involved two stages:

- Stage 1: baseline review stage; reviewing two non-participants' urodynamic traces from all participating sites.
- Stage 2: trial data review stage; reviewing a random selection of participants' urodynamic traces from each participating site.

Each stage involved a review by a panel of two experts which consisted of the urodynamics engineering expert (FUTURE co-applicant) and one of the clinical co-applicants on the trial.

Stage 1: baseline review

The trial office requested all participating sites to send two anonymous urodynamic traces and the clinician reports including interpretation and diagnoses. These two traces were from their clinical practice prior to being accepted as a collaborating site (i.e. not FUTURE trial participants). Having confirmed anonymisation, the QA manager sent them to two reviewers from the QA review panel. Reviewers commented on the quality of the urodynamics technique and trace interpretation. The feedback was sent back to each site, including any advice and recommendations for improving urodynamics performance for the trial urodynamics stage.

If the reviewers raised minor issues with either the performance or the interpretation done by the site, the trial office arranged further discussion and clarification with the relevant site. If a 'red flag' was raised (defined as anything above a minor comment within the filling phase), the FUTURE chief investigator (subspecialist urogynaecologist) further reviewed the urodynamics trace and report, re-discussed with reviewers if required and further discussed the concerns and the remedy plan with the PI in the relevant site. Training sessions by an expert reviewer from the review panel

TABLE 27 Key elements of the guide for urodynamic practice

1. Minimum equipment specifications were given:
   - A uniform brand of equipment was not required.
   - The specification of the urodynamics machines should meet the ICS guidelines on urodynamic equipment[102] (a detailed inspection of conformity was not deemed necessary).
2. Prior to performing the first randomised urodynamics test within the FUTURE trial, collaborating sites were required to undertake urodynamics machine calibration checks for measurements.
3. Clear guidance for urodynamic trace marking was developed to standardise the points used for data in each study and make central reading/audit of traces more reliable.
4. Guidelines were given for the core elements of good urodynamics practices, including:
   - Zeroing to atmosphere
   - Filling rates
   - Trace printing order and scaling
   - Resting pressure ranges
   - Regular pressure transmission checks
5. A web-based training on best urodynamics practice was available for collaborating sites.
6. An expert clinical engineer (co-applicant) provided one-to-one support for collaborating sites if/when required.

were offered to support the performance and interpretation of urodynamics within the trial. These sites received closer monitoring within the trial (*Figure 15*).

Stage 2: trial data review

For every participant randomised to the urodynamic and CCA arm (referred to as the urodynamics arm), the site uploaded a copy of the urodynamics trace onto the trial website (with the clinician report) and completed the FUTURE urodynamics CRF (see www.fundingawards.nihr.ac.uk/award/15/150/05). Once sites had uploaded 10 traces, two were randomly selected for review by the review panel (random 20% check). However, for sites that recieved a 'red flag' at baseline (see *Figure 15*), two urodynamic traces were randomly selected after five traces had been uploaded.

The selected traces were validated and anonymised by the trial office and, with a copy of the urodynamics CRF, submitted to the urodynamics QA manager. The urodynamics QA manager co-ordinated the process thereafter: submitting the trace and urodynamics CRF to two members of the review panel; noting any concerns raised by the reviewer(s) and any actions required by site; co-ordinating the involvement of the chief investigator (similar to the baseline stage) and developing feedback to sites. If minor concerns or issues were identified by the reviewer(s), these were discussed with sites, a consensus was reached and the database updated as required. In situations where there was no response from the site, the chief investigator undertook a further review of the trace and urodynamics CRF, and the database was updated by the trial office as required. These decisions were recorded on a file note and communicated to the site by e-mail.

During the trial, the urodynamic QA reviewers pro forma was developed (see www.fundingawards.nihr.ac.uk/award/15/150/05) to streamline the QA process.

Results

Stage 1: baseline review

One hundred and twenty-two anonymous urodynamic traces and reports were reviewed by two reviewers from the FUTURE team: two urodynamic traces from each site (these were not trial participants, as explained above):

- Seven sites (6%) had minor concerns raised regarding the urodynamic technique/performance. The CI had discussion with the site and agreed on steps for improvement.

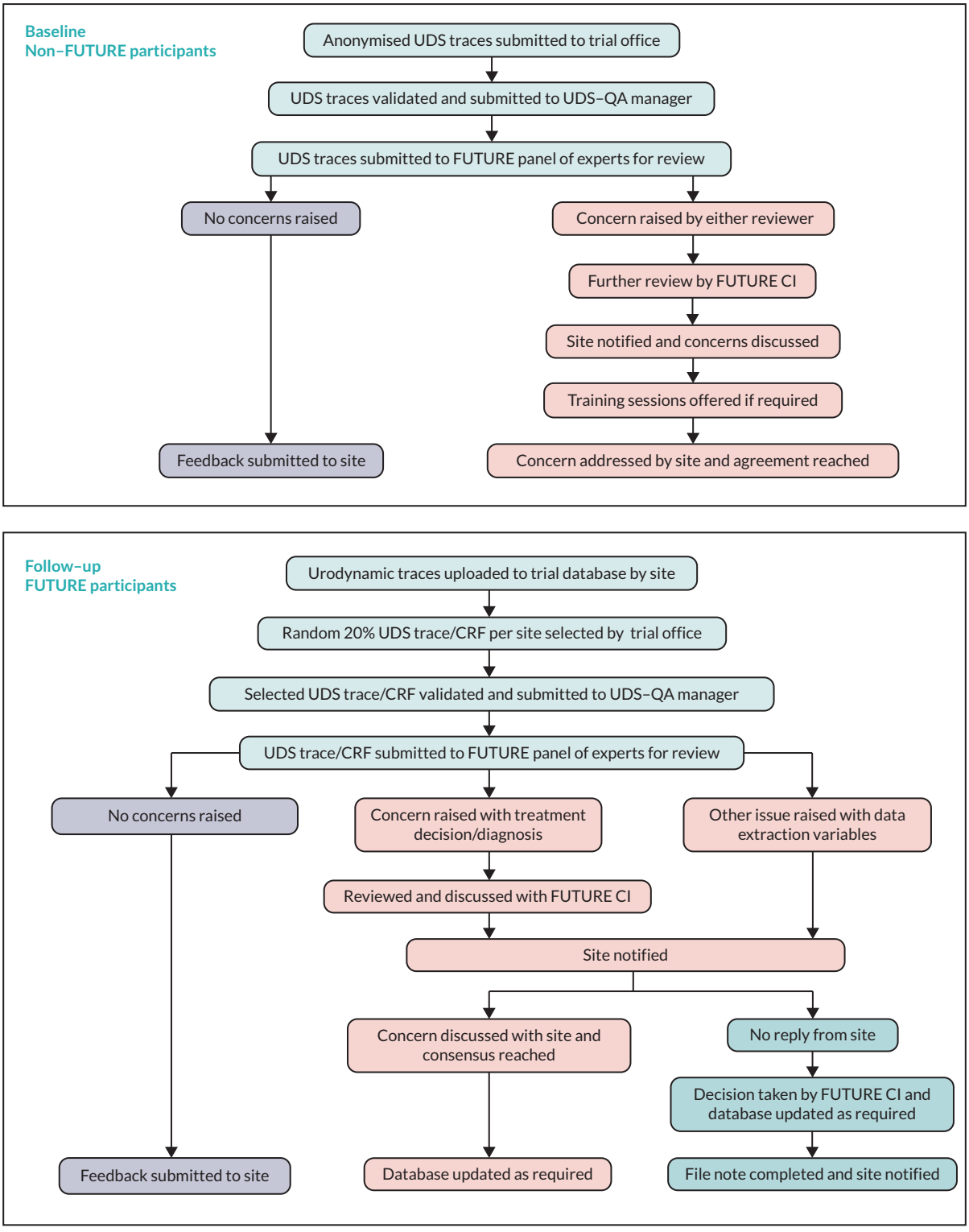

FIGURE 15 Urodynamics QA flow chart. UDS, urodynamics.

- Three sites (5%) were 'red flagged' by the reviewers in terms of the urodynamics technique which may have impacted on the quality of the urodynamics traces and results. The chief investigator arranged site training with an expert reviewer within the team.
- The remaining urodynamic traces and report had no concerns or a minor concern raised. This feedback was passed to the sites by e-mail.

Stage 2: trial data review

One hundred and twenty-four anonymous randomly selected urodynamic traces and CRFs from trial participants were reviewed from 61 sites. Four sites did not submit any urodynamic traces because they did not have anyone at their site randomised to the urodynamics arm.

The number of urodynamic traces and CRF reviewed per site were as follows:

- 27 sites had 1 urodynamic trace/CRF reviewed
- 20 sites had 2 urodynamic traces/CRFs reviewed
- 6 sites had 3 urodynamic traces/CRFs reviewed
- 5 sites had 4 urodynamics traces/CRFs reviewed
- 1 site had 5 urodynamic traces/CRFs reviewed
- 1 site had 6 urodynamic traces/CRFs reviewed
- 1 site had 8 urodynamic traces/CRFs reviewed.

Of the 124 urodynamic traces/CRFs that were reviewed by the panel:

- 60 urodynamic traces/CRFs (48%) received reviewers' feedback that was in full agreement with the site in both diagnosis and data entry; therefore, no further action was required.
- 47 urodynamic traces/CRFs (38%) required minor action, generally an update to the volumes recorded during the voiding phase, which were of limited relevance to the urodynamics diagnosis. The trial office contacted the sites for clarification and the database was updated accordingly.
- 16 urodynamic traces/CRFs (13%) were considered by the reviewer(s) to be suboptimal:
  - 2/16 the reviewers reported the quality of the scan as poor. The trial office contacted the site, who provided clearer traces.
  - 4/16 had reviewer comments on axis scales and 6/16 had reviewer comments on the placement of event markers. These comments were relayed to the sites and CRF data adjustments recommended, and the database was updated accordingly.
  - 8/16 had reviewer comments on poor QA checks during the study, and 9/16 had comments on resting pressures or zero setting. Again, these comments were fed back to sites for technique improvement.

- Two urodynamic traces/CRFs (2%) were considered to deviate from the FUTURE treatment pathway (e.g. recommending BoNT-A treatment in absence of DO). After further review by the chief investigator, file notes were added by the trial office to indicate the pathway deviation.
- Five urodynamics traces/CRFs (4%) had disagreement by both reviewers regarding the clinical diagnosis recorded by site. The chief investigator discussed this with the PIs in the relevant site and a change of diagnosis was agreed. The trial office updated the database on behalf of the sites.

Conclusions

The baseline review process for the urodynamic traces prior to the sites commencing recruitment within the FUTURE trial was very helpful to address different urodynamic techniques and procedures within the collaborating sites. The training and advice provided by the urodynamics engineering expert (co-applicant), to improve the quality of the urodynamics and the process of interpretation, were well received by all collaborating sites.

In the pre-trial review of 122 urodynamic traces and reports, it was reassuring that 116 (95%) had acceptable quality of traces. The remaining three sites (5%) received direct advice and training before recruitment began.

The presence of a well-defined and agreed QA system within the trial was key for keeping all collaborating sites aware that the quality of their urodynamics process was regularly monitored in a supportive and constructive way.

Of the 124 randomly selected traces reviewed from the trial data, 107 (86%) had no or only minor comments raised by the reviewers. Eight (6%) urodynamic traces/CRFs had questions raised regarding the QA checks (considered suboptimal traces by reviewers) and five urodynamic traces/CRFs (4%) required a diagnosis change following their review.

To keep the standardisation of the urodynamics performance and to gain QA, the feedback provided by the two review panel members was vital. In addition, the sites' responses and communication were key to reaching the aim of consistency and quality in the urodynamic interpretation, thus making the diagnosis in the trial more accurate and meaningful.

Chapter 8 Discussion

Summary of results

The FUTURE study is the largest RCT to date evaluating the clinical and cost-effectiveness of urodynamics investigation in the treatment pathway of women with refractory OAB or urgency-predominant MUI. FUTURE compared treatment outcomes in women following urodynamics plus CCA (referred to as the urodynamics arm) versus CCA only (referred to as the CCA only arm). The results confirm that the participant-reported success rates following treatments in women who underwent urodynamics and CCA were not superior to those who underwent CCA only [adjusted OR 1.12 (95% CI 0.73 to 1.74); $p = 0.601$]. We undertook sensitivity analyses and further per protocol analyses and the effect sizes were consistent with the main ITT estimates, providing confirmation and confidence in the results.

The results are consistent with Rovner *et al.*, where 331 patients (male and female) were randomised to receive various doses of BoNT-A treatment versus placebo.[50] All participants underwent baseline urodynamics and 75% had proven DO. They reported that patients with DO at baseline experienced similar reductions in the primary efficacy endpoint (mean change in weekly frequency of UUI episodes from baseline to week 12) compared with those without DO at baseline. However, their RCT was an efficacy study of BoNT-A versus placebo and the above comparison was a subgroup analysis and hence did not have sufficient power to detect significant differences between these relatively small subgroups. Nevertheless, they concluded that the similarity in symptom improvement between patients with refractory OAB with/without evidence of DO on urodynamics suggests it is not necessary to confirm DO using urodynamic testing prior to initiating BoNT-A treatment. In their study, patients with refractory OAB benefited from BoNT-A treatment regardless of baseline urodynamics diagnosis of DO. Similarly, Groenendijk *et al.* analysed the outcomes for all 111 women who underwent SNM and showed a statistically significant improvement in first sensation and maximum filling volume in women with UUI with or without baseline DO following SNM.[56] They concluded that women with UUI but no DO are at least as successful as women with UUI and DO and therefore baseline DO should not be a prerequisite selection criterion for using SNM.

Participant-reported success rates

The primary outcome in FUTURE was the proportion of participants who reported success at their final follow-up time point (15 or 24 months post randomisation). Success was a participant response of either 'very much improved' or 'much improved' to the question 'How would you describe your urinary/bladder problems (urgency and/or incontinence) now compared to when you joined the study?' on the PGI-I assessment tool (i.e. comparing their symptoms in the last 2 weeks prior to completing the questionnaire to their symptoms on the day they were randomised). We considered all other responses ('improved', 'same', 'worse', 'much worse' and 'very much worse') as unsuccessful.

Our participant-reported success rates in both trial arms were noted to be lower than those reported in the literature. At the final follow-up time point, 117 women (23.6%) in the urodynamics arm and 114 women (22.7%) in the CCA only arm reported success as per our definition; that is, 'very much improved' or 'much improved'. The majority of participants in the FUTURE trial received BoNT-A treatment ($n = 620$).

Brubaker *et al.* conducted a RCT evaluating BoNT-A treatment against placebo, in women with refractory OAB and associated DO on urodynamics, and showed that approximately 60% of women who received BoNT-A had a positive clinical response based on the PGI-I.[49] However, they defined participant-reported success as a PGI-I score of 4 or greater at least 2 months after injection; that is, they defined success as 'very much improved', 'much improved' or 'improved' 2 months post treatment. Similarly, Chapple *et al.* (2013), in a double-blind, placebo-controlled RCT, showed that BoNT-A was associated with participant-reported success rates of 62%, where they defined success as 'improved and greatly improved' on the Treatment Benefit Scale – a four-point scale ('greatly improved', 'improved', 'no change' and 'worsened') at 3 months post treatment.[51] In the Chapple *et al.* RCT 86% of the participants were women.

The reasons behind the apparent lower success rates in FUTURE are therefore trifold: the other studies in the literature (1) used a less strict definition of success, that is, 'improved' was classed as success, (2) had significantly shorter follow-up duration and (3) assessed the outcomes at set time points triggered by receiving the BoNT-A treatment, as compared to set time points post randomisation (as in FUTURE). The latter is especially important when considering BoNT-A treatment due to the transient nature of its success (i.e. improvement tends to wane 4–6 months after the injection). Unlike the above studies which were designed to assess the efficacy of BoNT-A treatment, FUTURE was as a pragmatic RCT evaluating the effectiveness of urodynamics in women with refractory OAB/urgency-predominant MUI. The treatment pathways therefore included other options of management, such as surgery for SUI, SNM, PTNS and others, including no treatment (see www.fundingawards.nihr.ac.uk/award/15/150/05). Hence it was necessary to set up the follow-up points post randomisation.

The above challenges were, however, identified early in the trial by the PMG and the independent DMC and to address these:

- A secondary analysis utilising a similarly less strict definition of success on PGI-I was included; that is, 'very much improved', 'much improved', and 'improved'. Inclusion of 'improved' as a successful outcome had the effect of increasing the number of participants reporting success at the last follow-up time point in both the urodynamic arm (43.8%) and the CCA only arm (41.6%). However, the effect size was similar to our primary analysis [OR 1.14 (95% CI 0.79 to 1.65); $p = 0.469$].
- An additional PGI-I question specific to women who underwent BoNT-A treatment was introduced, asking them to rate their symptoms 2 months after receiving treatment, that is, short term post-treatment assessment as used by Brubaker *et al.* and Chapple *et al.*[49,51] The participant responses to this question would therefore best represent the participant-reported success rates for the subgroup who received BoNT-A treatment. Using the primary definition of success on PGI-I, the participant-reported success rates were 63.8% versus 60.0% [OR 1.17 (99% CI 0.73 to 1.89); $p = 0.518$] in the urodynamics arm and the CCA only arm, respectively. Using the less strict definition of success (inclusion of 'improved') the participant-reported success rates were 83.3% versus 76.4% [OR 1.47 (99% CI 0.82 to 2.63); $p = 0.195$] in the urodynamics arm and the CCA only arm, respectively. These results are comparable to those reported by Brubaker *et al.*[49] and Chapple *et al.*[51] The effect sizes for both analyses were similar to our primary analysis.

The above extra analyses provide further reassurances of the robustness of the results of the primary outcome analysis.

Participant-reported success rates at earlier time points (3 and 6 months) showed significant differences between groups favouring CCA only, which was consistent using the original and less strict definition of success. However, by the last follow-up time point, the difference had disappeared and there was no significant difference between groups. The main explanation is that women receiving CCA only were more likely to receive their treatment without the delay of waiting for the urodynamics test, and therefore experienced earlier improvement in their symptoms. In women receiving BoNT-A treatment, the mean time to receiving the first dose of BoNT-A was 234.3 days in the urodynamics arm versus 188.4 days in the CCA only arm.

Recruitment

One thousand one hundred and three women were randomised, slightly over the recruitment target of 1096, making FUTURE the largest trial to date worldwide to recruit women with refractory OAB and the only one to date to evaluate the clinical and cost effectiveness of urodynamics in women with refractory OAB. The successful recruitment to target has been described by both the independent TSC and the DMC as a big achievement given the halt to all non-COVID-19 research in the UK from March 2020 till late 2020. A more detailed description of the impact of COVID-19 on the FUTURE trial in terms of recruitment, data collection and analyses of outcomes is outlined later in this chapter.

Response rates

Questionnaire response rates were over 90% for the 6-, 15- and 24-month post-randomisation questionnaire, an excellent achievement in these types of trials and comparable with the three largest studies assessing the effectiveness of BoNT-A as a treatment for refractory OAB. Chapple *et al.* randomised 548 patients; 89% completed the 6-month follow-up timepoint.[51] Tincello *et al.* recruited 240 patients; 83% completed the 6-month follow-up time point (n = 199).[102] In Rovner *et al.*, 87% (272/313) completed the 36-week follow-up time point.[50] In Brubaker *et al.*, a total of 43 subjects were randomised, including 28 to BoNT-A and 15 to placebo; the study was stopped prematurely due to the higher-than-expected rates of increased PVR and associated UTIs.[49]

Choice of the primary outcome

The primary outcome measure in FUTURE was participant-reported success at 15 months post randomisation as measured by PGI-I.

We surveyed surgeon opinions (urologists/urogynaecologists) in 45 units at the time of trial design and the vast majority recommended follow-up time points at 6 and 15 months post randomisation. These two timings are appropriate for measuring the outcomes of treatments for refractory OAB: 6 months is adequate to capture participant-reported and objective outcomes and early AEs for each treatment (such BoNT-A or SNM), while 15 months post randomisation is appropriate to compare the overall outcomes (participant-reported/objective success rates, participant satisfaction, AEs, further treatment, cost–utility and cost-effectiveness) between trial arms.

The PGI-I is a global index that is widely used to rate the response of a condition to a therapy (transition scale). It is a simple, direct and easy to use scale that is intuitively understandable to clinicians and patients.[103] The PGI-I has excellent construct validity compared to various assessment variables: incontinence episode frequency, the incontinence HRQoL questionnaire, and fixed volume (400 ml) stress pad test.[104]

In a benchmark study, Yalcin and Bump reported a secondary analysis of data from two double-blind, placebo-controlled clinical trials (n = 1133) that evaluated treatment of women with predominant SUI.[105] The authors showed that significant correlations ($p < 0.0001$) were observed between the PGI-I response categories and three independent measures of improvement in SUI (0.49, 0.33 and −0.43 with incontinence episode frequency, stress test and Incontinence HRQoL Questionnaire results, respectively). This important study established the construct validity of the PGI-I for the evaluation of the baseline severity and treatment response in women with UI.

The PGI-I has been widely used in clinical trials assessing surgical and conservative interventions for UI in women:

- The RELAX trial evaluated the PGI-I as an outcome assessment tool in women with refractory OAB symptoms requiring BoNT-A treatment (i.e. a similar cohort to the FUTURE study).[102] The results showed that 'the PGI-I scales are robust and valid instruments to assess disease severity, bother and improvement after treatment in women with detrusor overactivity'.
- Brubaker *et al.* used PGI-I as the primary outcome in their RCT evaluating BoNT-A treatment versus placebo in women with refractory OAB.[49] The results showed a successful outcome in approximately 60% of the women who received BoNT-A treatment. The authors showed that PGI-I was able to detect differences in responses between groups.
- The PGI-I was utilised in the SIMS RCT (n = 600), evaluating surgical interventions for SUI in women.[106] The results showed excellent response rate at 1- and 3-year follow-up.
- Two clinical trials on 10-year outcomes following surgical treatment of SUI in women utilised PGI-I as their primary participant-reported outcomes.[107,108]

One study compared the PGI-I versus the change in ICIQ-SF score for women undergoing UI or pelvic organ prolapse surgery; and reported that PGI-I may overestimate participant-reported success.[109] The accompanying editorial

questioned their methodology of the arbitrary conversion of individual scores for both questionnaires to the same scale as the numerical values assigned to each category in the underlying items.[110]

Our team has considered the use of disease-specific questionnaires (such as ICIQ-OAB or ICIQ-LUTSQoL) and the change in the post-treatment scores as the primary outcome. However, such an approach would have a number of potential drawbacks: (1) OAB-specific questionnaires/scores would inevitably miss the impact of the interventions on other urinary symptoms, such as new-onset or worsening of pre-existing stress incontinence and/or voiding dysfunction; (2) the post-intervention score-change that represents minimal clinical important difference was found to differ between studies, hence is not considered reliable.[111,112] We have therefore included these validated questionnaires as secondary outcomes.

In summary, PGI-I provides a robust validated and more global review of the treatment outcome and is more encompassing of the range of benefits and potential harms.[110] We used appropriate disease-specific symptom severity and HRQoL questionnaires as secondary outcomes.

Subgroups and participant-reported success rates

We have further analysed the participant-reported success rates in both groups according to the baseline clinical diagnosis of OAB and urgency-predominant MUI. In line with the main results, at the 3-month follow-up time point, women in the CCA only arm had significantly higher participant-reported success rates in both subgroups. However, at the final time point, the difference in both subgroups was not significant. The subgroup effects of 1.14 (99% CI 0.33 to 3.90), $p = 0.788$, and 1.07 (99% CI 0.39 to 2.95), $p = 0.861$, for the original and less strict definitions of success respectively show that there is no evidence of a significant difference in the effect of urodynamics between participants with a baseline clinical diagnosis of OAB compared to urgency-predominant MUI.

As the majority of women in FUTURE received BoNT-A treatment, we undertook a further post hoc analysis to evaluate the effect of urodynamics in the cohort of participants who underwent BoNT-A treatment according to their baseline clinical diagnosis (OAB vs. urgency-predominant MUI). The participant-reported success rates 2 months following BoNT-A treatment showed urodynamics to be more effective in the urgency-predominant MUI group compared to OAB, but the subgroup interaction was not significant [OR 0.74 (99% CI 0.19 to 2.96); $p = 0.581$].

Other studies in the literature did not specifically make a similar comparison. Tincello *et al.* tested whether any baseline covariates had an impact on outcomes following BoNT-A treatment.[102] They found the only associated factor was severity of frequency at baseline: for each additional voiding episode at baseline, they showed an additional 0.37 (95% CI 0.17 to 0.58; $p < 0.001$) reduction in voiding frequency.

The small number of women in the subgroups receiving other treatments [PTNS (48 women), SUI (21 women) or SNM (19 women)] would make comparison of outcomes by group clinically and statistically non-meaningful.

Urinary symptoms

We analysed urinary symptoms at baseline and at the follow-up time points using the ICIQ-FLUTS and bladder diaries.

International Consultation on Incontinence Questionnaire female lower urinary tract symptoms

ICIQ-FLUTS is a validated symptom severity questionnaire for three domains: filling, voiding and incontinence. As expected, there was no improvement in the voiding domain score but slight deterioration. This is best explained by the fact that treatments for refractory OAB can relax the detrusor muscle in parallel to reduction in the sensitivity of the detrusor receptors. BoNT-A treatment is known to lead to an increase in PVR volumes and may require women to perform CISC to achieve complete bladder emptying. Rovner *et al.* reported a dose-dependent increase in PVR with BoNT-A treatment which declined steadily to week 36.[50] Tincello *et al.* showed that voiding difficulty requiring CISC was

reported by 16% of women in the BoNT-A group and by 4% of the placebo group [OR at 6 months 4.87 (95% CI 1.52 to 20.33); $p = 0.003$].[102]

In FUTURE it was reassuring to see improvement in both the filling and incontinence domain scores in both groups at the final time points compared to baseline. The between-group difference was significant only in the filling domain, favouring urodynamics. The filling domain best represents improvement in overall OAB symptoms (daytime/night frequency and urgency) while the incontinence domain reflects improvement in the frequency of the UI episodes.

We utilised two disease-specific assessment tools for OAB symptoms: the ICIQ-OAB scores and the UPS. At the final follow-up time point, ICIQ-OAB scores showed improvement in both groups compared to baseline, with no significant differences between the study groups. Similarly, the percentages of women reporting cure/improvement in urgency on the UPS were similar: urodynamics 45% versus CCA only 42%.

Bladder diaries

One-third of women in FUTURE completed the 3-day bladder diary at 6- and 15-month follow-up. Diaries represent excellent semi-objective assessments of various urinary symptoms, such as daytime/night frequency, urgency and its severity, UI episodes and their severity, number of pads and others. The baseline findings were similar to other RCTs in the literature which included women with refractory OAB: urgency and UI episodes were 7 and 4/day, respectively. Chapple *et al.* and Tincello *et al.* reported urgency episodes of ~9/day and 8/day and UI episodes of ~5/day and 6/day at baseline, respectively.[51,102] Rovner *et al.* reported a mean baseline daytime frequency of ~7 to 8/day.[50]

We analysed results for daytime frequency, nocturia, urgency episodes (mild/moderate and severe) and UI episodes (SUI/UUI). Apart from significant reduction in daytime frequency favouring CCA only at 6 months, all other parameters were similar between groups at 6- and 15-month follow-up.

There are no other RCTs in the literature that compared the impact of urodynamics versus CCA only on post-treatment urinary symptoms and parameters of bladder diaries. However, several studies assessed the impact of BoNT-A treatment in women with refractory OAB:

- UI episodes: Chapple *et al.* reported that participants with refractory OAB who received BoNT-A treatment perceived a significant overall improvement in their UI episodes: a mean decrease of 2.95 episodes.[51] The EMBARK study group assessed the efficacy of 100 units of BoNT-A in women with refractory OAB: they reported a mean 47.9% reduction of UI episodes at 3-month follow-up compared to baseline;[113] 60% of the participants who received BoNT-A treatment experienced ≥ 50% improvement in their UUI episodes.
- Urgency episodes: the EMBARK study also showed a mean reduction of 2.93 (95% CI −3.43 to −2.44) in urgency episodes at 3 months compared to baseline in participants who received BoNT-A treatment; this equated to a mean change of 30% reduction in urgency episodes.[113]

Health-related quality of life

We assessed the HRQoL in both groups using both general and disease-specific validated tools; hence the results are robust. There were no significant differences in any of the HRQoL scores between the groups. The ICIQ-LUTSQoL showed improvement in HRQoL compared to baseline in both groups. However, this was not reflected in improvement in the general HRQoL scores on the EQ-5D-5L.

The EMBARK study group utilised disease-specific questionnaires (incontinence QoL and the KHQ) and showed significant improvement in HRQoL compared to baseline in women with refractory OAB who received BoNT-A treatment (compared to placebo).[113] Similarly, Chapple *et al.* utilised both questionnaires and showed > 10 points improvement in all three domains of incontinence QoL questionnaire compared to baseline and > 5 points improvement in six out of seven domains in the KHQ in participants with refractory OAB who received BoNT-A treatment.[51] The single KHQ domain that did not show a clinically significant improvement was the 'General Health Domain', which is in agreement with the results where the general EQ-5D-5L scores did not show an improvement.

Adverse events

The current literature shows that from the patients' perspective, many describe urodynamics as invasive, intimate, embarrassing and a painful investigation associated with emotional distress.[62,63] Urodynamics is also associated with a risk of discomfort and UTIs.[52]

Reassuringly, in the FUTURE trial the AE rates were low and similar in the two groups. UTI was the most common AE (7%); as these were participant-reported it was difficult to establish which were related to urodynamics and which were related to BoNT-A. Reassuringly, other AEs reported following urodynamics were low, including pain/burning sensation (0.7%) and fainting (0.4%). The most commonly reported AEs were mainly those expected after BoNT-A treatment, as it was the most commonly utilised treatment; the use of long-term prophylactic antibiotics was reported in 7% and CISC in 5% of participants. Buttock numbness after SNM occurred in one participant. The Chapple *et al.* results showed 'uncomplicated UTI' as the most frequently reported AE, with only one case of complicated UTI, which occurred approximately 4 months after BoNT-A treatment.[51]

This study results showed nine SAEs during the follow-up period, including five unrelated deaths and two CISC. CISC is not normally classed as a SAE in clinical practice, hence in our opinion there were only two SAEs in FUTURE that were serious, related and expected; a case of upper UTI following BoNT-A that required hospitalisation and a general-anaesthetic-related complication following SUI surgery. In addition, limb weakness was reported (as an AE) by 2.2% of participants, which is relatively higher than other studies in the literature; these could be classified as AE related to BoNT-A treatment. In the RELAX study, there were three BoNT-A-related SAEs: two women reported generalised muscle weakness severe enough to interfere with daily activities, and one woman suffered a bronchopneumonia within 3 weeks of the BoNT-A injection.[102]

Impact of urodynamics on clinical decision-making

In order to answer this question, we analysed the results for the 499 participants who underwent urodynamics within FUTURE to answer two important questions:

1. Did urodynamics change the baseline clinical diagnosis?

Of the 499 participants with refractory OAB symptoms who underwent urodynamics, a diagnosis following urodynamics was available for 494 participants: 58% of the participants were diagnosed with DO and/or DOI, 13% had USI, 8% had urodynamics MUI and 21% had no evidence of USI or DO.

When adjusted for the baseline clinical diagnosis:

- in the group of participants with a baseline diagnosis of OAB, their urodynamics diagnoses were DO/DOI in 62.3% of cases, MUI in 6.2%, no evidence of USI or DO in 21.9% and USI in 8.3% of cases
- in the group of participants with a baseline diagnosis of urgency-predominant MUI, their urodynamics diagnoses were DO/DOI in 48.6% of cases, MUI in 10.9%, no evidence of USI or DO in 18.3% and USI in 21.7% of cases.

The results therefore showed that DO/DOI was not detected on urodynamic assessment in 34% of women with a clinical diagnosis of refractory OAB/urgency-predominant MUI. These findings are consistent with previous literature showing urodynamics fails to show evidence of DO in up to 45% of women with OAB.[60] In the latter, they assessed urodynamics diagnoses in the general population of women with OAB as compared to FUTURE where the cohort of women had refractory OAB.

One in five women in both groups had no evidence of either USI or DO on urodynamics; that is, the urodynamic test did not make any advances in diagnosis of their condition. In clinical practice, these women would receive symptomatic treatment according to their predominant symptoms and CCA diagnosis.

The results also showed that urodynamics clearly changed the diagnosis in 13% of women with refractory OAB/urgency-predominant MUI to USI. More women in the urgency-predominant MUI group were likely to be diagnosed with USI compared with women with a baseline clinical diagnosis of OAB (22% vs. 8%). This would have the potential to change the management plan to USI surgery according to clinical practice and the study treatment pathways, especially knowing that participants in FUTURE would have failed conservative treatment in the form of supervised PFMT prior to randomisation.

2. Did the clinicians make the treatment decisions based on the urodynamics diagnosis where it was different to the baseline clinical diagnosis?

In total, 65 women were diagnosed with USI in the urodynamics arm. Interestingly, only 20% (*n* = 13) had a treatment decision to undergo SUI surgery, while 37% (*n* = 24) had a treatment decision to undergo BoNT-A treatment. The remaining participants had other treatment decisions that were predominantly conservative.

By the final follow-up time point, 54/65 participants had received treatment and only 24% (*n* = 13) had received SUI surgery, while 39% (*n* = 21) received BoNT-A and a further 37% received treatment directed to their OAB symptoms, such as medical treatment, PTNS and cysto-distention.

The above clearly shows that among women with refractory OAB/urgency-predominant MUI at baseline who were subsequently diagnosed with USI on urodynamics, only one in five had a treatment decision according to their urodynamics diagnosis. In addition, by the final follow-up time point, only one in four of the participants received surgery for USI. Obviously, there may be more participants awaiting surgery for USI due to the COVID-19-related long waiting lists and/or participants who will undergo such treatments in the future.

Nevertheless, these results clearly indicate that clinicians are heavily influenced by their baseline clinical assessment, and a clear urodynamics diagnosis that contradicts this will not necessarily change their management decision. Similarly, in an observational study within the BUS RCT, 666 women with non-refractory OAB underwent urodynamics. Their results showed that clinicians and patients appeared to be guided in part by the urodynamics diagnosis in selecting treatment options.[52]

One explanation is the clinician's awareness of the limitation of urodynamics in detecting DO in women with OAB. They are also fully aware that the accuracy of urodynamics relies on well-calibrated equipment, the experience of investigators and their objective interpretation of subjective parameters. Hence the standardisation of the test is difficult and is affected by the wide variation in staff practice and type of equipment used.[61]

We assessed the clinical outcomes in the group of participants with baseline clinical diagnosis of MUI which was later changed to USI following the urodynamic assessment (*n* = 65). The participant-reported success rate at the final follow-up time point was 17% compared to 24% in the full FUTURE cohort (i.e. only one in six participants reported being 'very much improved or 'much improved'), rising to 37% (compared to 44% in the full FUTURE cohort) when using the less strict definition of success on PGI-I (inclusion of the response 'improved').

Of those who underwent SUI surgery, the participant-reported success rate was available for 11/13 participants, with only one participant meeting the definition of success, that is, 'very much improved' or 'much improved' (9%). These results show a poor success rate for participants with refractory OAB/urgency-predominant MUI who are diagnosed with USI on urodynamics and subsequently undergo surgical treatment for SUI. In the recent SIMS trial, participant-reported success rates following various mid-urethral slings were 77% at a similar 15-month follow-up time point and a similar definition of success ('very much improved'/'much improved') on PGI-I.[106]

The main explanation is that participants with a USI diagnosis in FUTURE are a different cohort of women, with baseline refractory OAB symptoms. One possible explanation for poor outcomes following SUI surgery in the participants with a USI diagnosis is that they were primarily due to the failure of urodynamics to show concomitant DO/DOI. If DO/DOI was shown, these participants would have undergone treatment directed to their predominant clinical symptoms (i.e. BoNT-A, SNM or PTNS). However, this explanation is challenged by the fact that in the CCA only arm more participants

received BoNT-A treatment [72% (*n* = 343) vs. 59% (*n* = 277)]; however, this was not associated with significantly better participant-reported success rates in the CCA only arm.

It is important to highlight the small number of participants who received surgery for SUI in FUTURE making it difficult to draw a robust conclusion.

In FUTURE, participants in the urodynamics arm underwent fewer invasive procedures. However, participant-reported success rates were not superior to CCA only. The BUS study economic evaluation modelling suggested that urodynamics can be a cost-effective diagnostic strategy in women with predominant symptoms of refractory OAB, based on fewer women undergoing invasive treatment in the urodynamics group and a possible small reduction in clinical effectiveness.[52] In contrast with this, the FUTURE trial confirmed no reduction in clinical effectiveness in the urodynamics group.

Quality assurance

Concerns had been raised previously in the literature about the impact of the quality of urodynamic studies on the reliability of diagnostic results.[99] A 'think tank' had considered it was clear that technique affects the quality of a urodynamic test, and with other factors it will affect the utility and perceived value of that test.[99]

A robust methodology for obtaining a measure of QA was therefore developed for FUTURE to reduce the potential variability of urodynamic assessments. The key elements included developing a robust protocol for urodynamic testing based on the ICS Good Urodynamics Practices (2002) and sharing this protocol with all sites from time of invitation to participate. We evaluated urodynamics traces from all sites prior to participation and shared the assessment and action plan (if required) with them. Throughout the trial, all sites submitted the urodynamics traces/reports that they performed, and the trial office arranged anonymous independent structured central review of randomly collected urodynamic data from each site. Online training and one-to-one training with experts were available and utilised as required. Full details are described in *Chapter 7*.

However, as a pragmatic effectiveness study, the role of the QA process was not to force departments into compliance with a rigid protocol, but to ensure that the data used for analysis were based on a reasonable level of assurance for its quality yet reflected the standard current clinical practice in the UK. For example, a uniform brand of urodynamics equipment was not required, but the capacity of machines was specified according to the ICS Guidelines on Urodynamic Equipment.

The presence of a well-defined and agreed QA system within FUTURE was key for keeping all collaborating sites aware that urodynamics was regularly monitored in a supportive and constructive way. The response and engagement from our collaborating sites were variable, but as a whole were reasonable, especially given we had over 60 participating sites representing all types of practice in the UK. It was reassuring to see that 95% of pre-trial submitted traces were of acceptable quality to our expert panel. During the study the urodynamics diagnosis was changed for five participants following the QA process and discussion with the local team.

Over 60 sites from all four nations in the UK participated in FUTURE, representing urology, gynaecology, tertiary centres, district general hospitals and teaching hospitals. Our QA system represented a key strength in ensuring the generalisability of the results and enabled the FUTURE trial to ensure a reasonably high-quality urodynamics practice while keeping the ethos of an effectiveness pragmatic study that represents the standard clinical practice in the UK.

Qualitative study

One strength of the FUTURE trial was the embedded qualitative study. The study findings confirm previous findings in this area related to women undergoing urodynamics investigation, not only for investigation of refractory OAB.[96–98] Some studies found that women report urodynamic investigations to be uncomfortable or even painful, particularly

during the insertion of the catheter into the bladder. However, other research has suggested that the level of discomfort varies widely among women, and some may not experience any discomfort at all.

Additionally, some women have reported feeling embarrassed or anxious during the test, particularly if it was their first time undergoing a urodynamic investigation. External influences include the type of catheter used, positioning during the test, skill of the clinicians, age, medical history and previous experiences of medical investigations. As with the study results, urodynamics is generally considered acceptable and it is important that healthcare staff support women to minimise associated discomfort or anxiety. Crucially, counselling is vital and the voices of women with lived experience included in this report will be extremely valuable in fully informing women about their assessment/investigation to enable them to prepare appropriately.

Cost-effectiveness

Urodynamics is shown to be more costly, principally due to the testing itself and more clinic visits. There is evidence of greater numbers of interventions for SUI in patients undergoing urodynamics, but all other effects are highly uncertain, and not statistically significant. There is no clear evidence of differences in HRQoL (as measured by the EQ-5D-5L) at any time point, nor in total QALYs. The higher mean costs and QALYs lead to urodynamics not being cost-effective at a funding threshold of £20,000 per QALY gained, with only a 34% chance of it being cost-effective. However, this is sensitive to imputation, with the complete case analysis showing a 67% chance of urodynamics being cost-effective. The subgroup analysis suggests larger health benefits for patients with an initial diagnosis of MUI, which is associated with a 72% chance of cost-effectiveness. This is principally due to the higher QALY gains in that participant group compared to participants with an initial diagnosis of OAB.

Further analysis of the effects that the 24-month data have on the results is warranted, as this leads to two methodological uncertainties. First, the pattern of missing data and its impact on costs and outcomes is more complex than is generally the case in RCTs. Second, the incorporation of both 15-month and 24-month data in the estimation of total costs and QALYs is based on a simple, additive specification. Alternative approaches to these issues are possible and need consideration.

Extrapolation of the estimated 24-month results using final treatment designations and long-term success rates taken from the literature reduce the chance of urodynamics being cost-effective further. This finding is driven by the higher rates of ongoing treatment with BoNT-A in the CCA group, to which the model applies favourable EQ-5D-5L values and long-term success rates (as sourced from FUTURE and our literature review, respectively). However, if the long-term success rates for BoNT-A are later found to be reduced, that will impact the long-term cost-effectiveness analysis.

Impact of the coronavirus disease-19 pandemic

The COVID-19 pandemic had an impact on the FUTURE trial in terms of recruitment, data collection and analysis of the trial results.

Recruitment

Recruitment to the FUTURE trial was paused in March 2020 due to the COVID-19 pandemic, at which point 1022 participants had been recruited: 93% of the overall target. Approvals to restart recruitment were obtained in August 2020 and the recruitment end date was extended to 31 January 2021. A further 81 participants (7.3% of the total randomised) were recruited after the pause; 43 to receive urodynamics and 38 to receive CCA only.

Data collection

The primary aim of the FUTURE trial was to assess participant-reported improvement in symptoms following treatment for refractory OAB. However, during the COVID-19 pandemic, routine NHS treatments were suspended, leading to treatment delays. As a result, some FUTURE participants received the 6- and 15-month post-randomisation questionnaires before treatment delivery.

Therefore, for participants whose treatment had been delayed because of the pandemic, an additional 24-month post-randomisation questionnaire was issued. This questionnaire contained the same suite of questions as the 15-month post-randomisation questionnaire and followed the same reminder system. A case-note review was also conducted for these participants at 24 months post randomisation.

A participant was deemed eligible for the additional 24-month questionnaire (i.e. their treatment was delayed) if they were randomised 6 months prior to the recruitment pause (September 2019 to March 2020; *n* = 207), no intervention (urodynamics or CCA-only) CRF had been completed prior to March 2020 (*n* = 13) and the site confirmed the participant was on the waiting list for treatment in March 2020 (*n* = 85). Therefore, 27.8% of the FUTURE cohort received the additional 24-month post-randomisation questionnaire.

Analysis of the trial results

The COVID-19 pandemic impacted on the analysis by delaying assessment and treatment. Therefore, the addition of the 24-month questionnaire benefited the analysis as participants' final outcomes were at the correct point in their treatment pathway and the number of participants who reported outcome data without having received treatment was reduced.

Another impact of COVID-19 was a higher rate of missing data. The analysis model used was planned in the protocol and pre-COVID-19 drafts of the statistical analysis plan with two additions. A dummy variable indicating a participant received a 24-month follow-up questionnaire and the time from randomisation to all observations used in the repeated-measures mixed model were also included. As recommended in Cro *et al.* (2020), multiple imputation with chained equations was used to explore the effect of missing data.[114] A variable indicating a participant's assessment or treatment was affected by COVID-19 was included in the imputation model. Sensitivity analyses for the effect of missing data using pattern-mixture modelling were also performed.

The adoption of two different lengths of follow-up poses additional problems for the cost-effectiveness analysis as both costs and QALYs are calculated as cumulative values over the follow-up period. As such, participants who are followed-up for longer necessarily generate higher costs and QALYs. Estimation of incremental costs and QALYs, therefore, needs to account for this through the inclusion of additional terms in the relevant regression analyses. In tandem with the associated patterns of missing data, there is some uncertainty relating to the best specifications for the regression and imputation. As such, further exploration of this is warranted.

COVID-19 also had a specific direct impact on the FUTURE trial in that the subgroup analysis comparing participants who started on BoNT-A to those who started on SNM could not be conducted due to the low number of participants who received SNM, nor was it possible to make the comparison of SNM and BoNT-A on participants whose treatment assessment was made using urodynamics.

Patient and public involvement

Pre-funding application and design of the research

Prior to the initial funding application, we established a collaboration with the largest relevant patient-support group in the UK to provide insights from the patient's perspective. The Bowel and Bladder Foundation advised on the treatment pathways, proposed assessment tools and outcome measures. However, they ceased operating in July 2016 prior to the funding start date.

Bladder Health UK were therefore approached and agreed to support the research by becoming a co-applicant and a member of the PMG, providing clear leadership on the patient perspective, and were integral to the development of the trial protocol and all the trial documents, including the patient information sheet, letters of invitation/reminders, participant questionnaires and the bladder diary.

Oversight of the study

One of the independent members of the TSC was a patient representative. The TSC met throughout the study and reviewed all study documentation, including patient-facing documents, newsletters and questionnaires that were sent to potential and recruited participants in FUTURE. In addition to being an integral part of the study oversight, they provided the following feedback when reflecting on their experience:

> *I enjoyed working with clinicians and others to simplify documentation to make it easier to understand, and I was gratified when my suggestions were embraced. I hope my input helped those patients taking part in the trial give proper, informed consent.*

Report writing, academic paper preparation and dissemination

The Bladder Health UK representative and the PPI partner on the TSC have contributed towards the preparation of the plain language summary and have been actively involved in discussions of the trial results with the TSC. They will continue to be involved in dissemination activities, including the dissemination of results to the FUTURE participants and academic papers.

Equality, diversity and inclusion

The participants in FUTURE were similar in age to the UK female population with OAB. They were recruited from over 60 sites from all four nations in the UK, representing urology, gynaecology, tertiary sites, district general hospitals and teaching hospitals.

The research team included representatives from Bladder Health UK, the largest bladder-patient-support charity in the UK. They, along with the PPI representative on the TSC, were actively involved throughout the trial contributing to the trial design, development of trial materials and contributing to discussions of the trial results, as well as preparation of the plain language summary.

The trial team represented a broad range of expertise in quantitative and qualitative methodologies. Less experienced members of the team were encouraged to lead discrete components of the study (under senior supervision) during all aspects of the trial, including start-up, recruitment, data collection and data cleaning.

Key strengths

Superiority design

A major issue in designing the trial was that urodynamics has become embedded in standard clinical care without a solid evidence base to support its routine or selective use, as highlighted by the NICE guideline.[3] Usually, when designing a study to test a standard of care, a non-inferiority design is used. In such a design it could be argued that if the removal of urodynamics preserved at least *x*% of the proven benefit of urodynamics, and by removing it the patient journey is made better, and/or safer, and/or cheaper, then the acceptable reduction (the so-called non-inferiority margin, 100 – *x*%) in the clinical effectiveness can be traded-off against these other benefits. However, if urodynamics has been accepted into practice without demonstrating its actual benefit over clinical assessment only, then it is not possible to set a credible non-inferiority margin. Instead, it seems imperative to go back one step in the evidence base and conduct the superiority-type design that has been missed.

The trial design also included a well-designed and adequately executed QA system, an embedded qualitative study to explore participants' experiences, and a parallel cost-effectiveness analysis, which are all key strengths of the FUTURE trial.

Large sample size and recruitment to target within reasonable time frame

To our knowledge, FUTURE is the largest RCT worldwide for evaluating the clinical and cost-effectiveness of urodynamics in women.

Independent data monitoring and Trial Steering Committees

The independent DMC and TSC met regularly throughout the study and were instrumental in successfully delivering the trial. The decision to introduce a secondary analysis considering 'improved' as success was a key decision supported by both committees.

Key limitations

The majority of participants in FUTURE underwent BoNT-A treatment, which can be seen as a limitation. While it represents the standard clinical practice in the UK, the small number of participants receiving other treatments made pre-planned secondary analyses for outcomes of SNM and PTNS not possible. In addition, we were not able to test the best sequence of treatments.

Follow-up was limited to 15 to 24 months; hence, we lack information on whether women in the CCA only arm would end up having urodynamics at a later stage, which will impact the clinical and cost-effectiveness results. Longer-term follow-up to 5 years is under way. Lastly, the impact of the COVID-19 pandemic led to a number of participants not receiving the intervention and or treatments during the original 15-month follow-up period. However, we were able to mitigate this to a great extent by excellent communication with our collaborating sites and introducing an additional follow-up time point at 24 months for participants who suffered these delays.

Key take-home messages

1. In women with refractory OAB/urgency-predominant MUI, the participant-reported success rates following treatment in women who underwent urodynamics and CCA were not superior to those who underwent CCA only [adjusted OR 1.12 (95% CI 0.73 to 1.74); $p = 0.601$]. Sensitivity analyses and further per protocol analyses showed similar effect sizes and provided confirmation and confidence in the trial results.
2. A secondary analysis with the inclusion of 'improved' as a successful outcome on the PGI-I had the effect of increasing the number of participants reporting success at the last follow-up time point. However, the effect size was similar to the primary analysis [OR 1.14 (95% CI 0.79 to 1.65); $p = 0.469$].
3. A secondary analysis asking women who underwent BoNT-A treatment to rate their symptoms 2 months after receiving treatment had the effect of increasing the number of participants reporting success; however, the effect sizes remained insignificant [OR 1.17 (95% CI 0.73 to 1.89); $p = 0.518$].
4. A secondary analysis of participant-reported success rates according to the baseline clinical diagnosis of OAB and urgency-predominant MUI, at the final time point, showed no evidence of a significant difference in the effect of urodynamics when using both the original and less strict definition of success [1.14 (99% CI 0.33 to 3.90); $p = 0.788$ and 1.07 (99% CI 0.39 to 2.95); $p = 0.861$], respectively.
5. Women in the urodynamics arm underwent fewer invasive procedures; however, participant-reported success rates were not superior to those in the CCA only arm.
6. Over 60 sites from all four nations in the UK participated in FUTURE, representing urology, gynaecology, tertiary centres, district general hospitals and teaching hospitals. Our QA system represented a key strength in ensuring the generalisability of the results and enabled the FUTURE trial to ensure a reasonably high-quality urodynamics practice while keeping the ethos of an effectiveness pragmatic study that represents the standard clinical practice in the UK.
7. The cost-effectiveness data showed that urodynamics had a 34% probability of being cost-effective at £20,000 per QALY gained. This probability reduced further when the results are extrapolated over the patients' lifetimes. In a subgroup analysis for participants with baseline clinical diagnoses of OAB and urgency-predominant MUI separately, the two groups of participants were found to have similar costs, but women with a baseline diagnosis of MUI had a notably greater gain in QALYs associated with urodynamics (0.053 vs. −0.010). This led to a lower ICER (£8357 per QALY gained) and a commensurately higher probability of being cost-effective at £20,000 per QALY (72%).
8. DO/DOI was 'not' detected on urodynamic assessment in 34% of women with a clinical diagnosis of refractory OAB at baseline. One in five participants had no evidence of USI or DO on urodynamics. In clinical practice, these

women would receive symptomatic treatment according to their CCA diagnosis. Finally, participants with a USI diagnosis had poor participant-reported success rates compared to the rest of the FUTURE cohort. Those who underwent SUI surgery had poor success rates, but the numbers were very low to make robust conclusions in this subgroup.

Conclusion

In women with refractory OAB/urgency-predominant MUI, the participant-reported success rates following treatment in women who undergo urodynamics and CCA are not superior to those who undergo CCA only, up to 15 months post randomisation. Significantly more women who undergo CCA only report earlier improvement in their symptoms. Urodynamics plus CCA is not cost-effective at a threshold of £20,000 per QALY gained.

Future research

1. Longer-term outcomes are being assessed up to 5 years to explore further treatments received in both arms and whether women in the CCA only arm undergo urodynamics later and to compare the participant-reported outcomes after longer-term follow-up in both groups.
2. It is clear from the results that women with urgency-predominant MUI have different outcomes. Similar findings are reported in the literature with regard to women with a baseline diagnosis of stress-predominant MUI having different outcomes following SUI surgery. Hence future research should assess the clinical effectiveness of urodynamics in women with MUI (both stress- and urgency-predominant MUI).
3. Once the results of the extended follow-up are available, a value-of-information analysis should be undertaken by updating the parameters within the cost-effectiveness model in order to help identify those research questions that are most valuable to commissioners.

Additional information

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Suzanne Evans (Bladder Health UK, PPI) has been involved as a PPI team member since conception of the trial, oversaw the conduct of the trial and the interpretation of results and the writing/editing of the report.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

Female Urgency, Trial of Urodynamics as Routine Evaluations received a favourable ethics opinion from the North of Scotland Research Ethics Committee on 27 March 2017 (REC reference number 17/NS/0018).

Information governance statement

The University of Aberdeen are committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation. The University of Aberdeen is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights, and the contact details for our Data Protection Officer here www.abdn.ac.uk/privacy.

Disclosure of interests

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Appendix 1 Additional information for baseline results

TABLE 28 Recruitment table

	Urodynamics	CCA only	Total
NHS Grampian	46 (8.3%)	46 (8.4%)	92 (8.3)
NHS Greater Glasgow & Clyde	33 (6.0%)	37 (6.7%)	70 (6.3)
The Leeds Teaching Hospitals NHS Trust	24 (4.3%)	25 (4.5%)	49 (4.4)
South Tees Hospital NHS Foundation Trust	22 (4.0%)	24 (4.4%)	46 (4.2)
East Sussex Healthcare NHS Trust	23 (4.2%)	21 (3.8%)	44 (4.0)
Stockport NHS Foundation Trust	22 (4.0%)	21 (3.8%)	43 (3.9)
University Hospital Southampton NHS Foundation Trust	20 (3.6%)	21 (3.8%)	41 (3.7)
Newcastle upon Tyne Hospitals NHS Foundation Trust	19 (3.4%)	21 (3.8%)	40 (3.6)
Manchester University NHS Foundation Trust	19 (3.4%)	18 (3.3%)	37 (3.4)
City Hospitals Sunderland NHS Foundation Trust	17 (3.1%)	17 (3.1%)	34 (3.1)
Hampshire Hospitals NHS Foundation Trust	14 (2.5%)	13 (2.4%)	27 (2.4)
The Pennine Acute Hospitals NHS Trust	14 (2.5%)	13 (2.4%)	27 (2.4)
NHS Lanarkshire	13 (2.4%)	13 (2.4%)	26 (2.4)
Liverpool Women's NHS Foundation Trust	11 (2.0%)	12 (2.2%)	23 (2.1)
Bradford Teaching Hospitals NHS Foundation Trust	11 (2.0%)	11 (2.0%)	22 (2.0)
Nottingham University Hospitals NHS Trust	11 (2.0%)	11 (2.0%)	22 (2.0)
Northern Health & Social Care Trust	10 (1.8%)	11 (2.0%)	21 (1.9)
Countess of Chester Hospital NHS Foundation Trust	11 (2.0%)	10 (1.8%)	21 (1.9)
North Bristol NHS Trust	10 (1.8%)	9 (1.6%)	19 (1.7)
Calderdale and Huddersfield NHS Foundation Trust	10 (1.8%)	9 (1.6%)	19 (1.7)
Cambridge University Hospitals NHS Foundation Trust	8 (1.4%)	11 (2.0%)	19 (1.7)
Salford Royal NHS Foundation Trust	10 (1.8%)	9 (1.6%)	19 (1.7)
Portsmouth Hospitals NHS Trust	10 (1.8%)	8 (1.5%)	18 (1.6)
Salisbury NHS Foundation Trust	9 (1.6%)	9 (1.6%)	18 (1.6)
NHS Forth Valley	8 (1.4%)	8 (1.5%)	16 (1.5)
Royal United Hospitals Bath NHS Foundation Trust	8 (1.4%)	7 (1.3%)	15 (1.4)
Brighton & Sussex University Hospitals NHS Trust	8 (1.4%)	7 (1.3%)	15 (1.4)
Oxford University Hospitals NHS Foundation Trust	9 (1.6%)	6 (1.1%)	15 (1.4)
St Helens and Knowsley Teaching Hospitals NHS Trust	8 (1.4%)	7 (1.3%)	15 (1.4)
NHS Fife	8 (1.4%)	6 (1.1%)	14 (1.3)
Kingston Hospital NHS Foundation Trust	6 (1.1%)	8 (1.5%)	14 (1.3)

continued

TABLE 28 Recruitment table (*continued*)

	Urodynamics	CCA only	Total
Norfolk & Norwich University hospitals NHS Foundation Trust	7 (1.3%)	7 (1.3%)	14 (1.3)
The Royal Wolverhampton NHS Trust	5 (0.9%)	8 (1.5%)	13 (1.2)
Mid Yorkshire Hospitals NHS Trust	7 (1.3%)	5 (0.9%)	12 (1.1)
South Tyneside NHS Foundation Trust	5 (0.9%)	6 (1.1%)	11 (1.0)
Airedale NHS Foundation Trust	4 (0.7%)	6 (1.1%)	10 (0.9)
Guy's and St Thomas' NHS Foundation Trust	4 (0.7%)	6 (1.1%)	10 (0.9)
Plymouth Hospitals NHS Trust	6 (1.1%)	4 (0.7%)	10 (0.9)
East Cheshire NHS Trust	5 (0.9%)	4 (0.7%)	9 (0.8)
NHS Lothian	4 (0.7%)	5 (0.9%)	9 (0.8)
Wrightington, Wigan and Leigh NHS Foundation Trust	4 (0.7%)	5 (0.9%)	9 (0.8)
Great Western Hospitals NHS Foundation Trust	4 (0.7%)	4 (0.7%)	8 (0.7)
Wirral University Teaching Hospital NHS Foundation Trust	2 (0.4%)	6 (1.1%)	8 (0.7)
Frimley Health NHS Foundation Trust	3 (0.5%)	4 (0.7%)	7 (0.6)
Northampton General Hospital NHS Trust	3 (0.5%)	4 (0.7%)	7 (0.6)
York Teaching Hospital NHS Foundation Trust	5 (0.9%)	2 (0.4%)	7 (0.6)
Bolton NHS Foundation Trust	4 (0.7%)	2 (0.4%)	6 (0.5)
Milton Keynes University Hospital NHS Foundation Trust	3 (0.5%)	3 (0.5%)	6 (0.5)
NHS Borders	3 (0.5%)	2 (0.4%)	5 (0.5)
North West Anglia NHS Foundation Trust	3 (0.5%)	2 (0.4%)	5 (0.5)
Royal Devon and Exeter NHS Foundation Trust	3 (0.5%)	2 (0.4%)	5 (0.5)
NHS Tayside	2 (0.4%)	2 (0.4%)	4 (0.4)
Royal Berkshire	2 (0.4%)	2 (0.4%)	4 (0.4)
Sheffield Teaching Hospitals NHS Foundation Trust	3 (0.5%)	1 (0.2%)	4 (0.4)
Buckinghamshire Healthcare NHS Trust	1 (0.2%)	2 (0.4%)	3 (0.3)
Cardiff & Vale University Health Board	2 (0.4%)	1 (0.2%)	3 (0.3)
Royal Cornwall Hospitals NHS Trust	2 (0.4%)	1 (0.2%)	3 (0.3)
NHS Highlands	3 (0.5%)		3 (0.3)
Maidstone and Tunbridge Wells NHS Trust	1 (0.2%)	2 (0.4%)	3 (0.3)
Basildon & Thurrock University Hospitals NHS Foundation Trust		1 (0.2%)	1 (0.1)
University Hospitals Coventry and Warwickshire NHS Trust	1 (0.2%)		1 (0.1)
Swansea Bay University Local Health Board		1 (0.2%)	1 (0.1)
University College London Hospitals NHS Foundation Trust		1 (0.2%)	1 (0.1)
	N = 553	*N* = 550	*N* = 1103

TABLE 29 Approached participants

	n (%)
Screened	3066 (100.0)
Randomised	1103 (36.0)
Not included	1963 (64.0)
Ineligible	1555 (50.7)
Patient declined	408 (13.3)

TABLE 30 Primary reasons for non-inclusion

	n (%)
Ineligible	1555 (100.0)
Predominant SUI symptoms	318 (20.5)
Other clinical diagnosis (not OAB or urgency-predominant MUI)	227 (14.6)
Did not meet eligibility criteria (failed conservative and pharmacological treatment)	181 (11.6)
Previous urodynamics in last 12 months	166 (10.7)
Previously treated with BoNT-A/SNM	140 (9.0)
Neurological disease (e.g. Parkinson, spinal injuries)	93 (6.0)
Bladder pain syndrome	78 (5.0)
Prolapse beyond introitus	64 (4.1)
Patient decision not to proceed with invasive treatment	58 (3.7)
Inability to give informed consent	48 (3.1)
Recurrent UTI where significant pathology not excluded	39 (2.5)
Pelvic malignancy or clinically significant pelvic mass	22 (1.4)
Previous pelvic radiotherapy	21 (1.4)
Clinical preference for urodynamics	20 (1.3)
Ineligible for other clinical reasons	18 (1.2)
Pregnant or planning pregnancy	17 (1.1)
Urogenital fistulae	16 (1.0)
Ineligible for other reason	15 (1.0)
Reason for ineligibility unknown	10 (0.6)
Age	4 (0.3)
Eligible but patient declined randomisation/participation	408 (100.0)
No reason given	120 (29.4)
Did not want to be randomised	90 (22.1)
Preference for a particular clinical pathway	66 (16.2)
Personal reason	49 (12.0)
Unable to contact after eligibility confirmed	42 (10.3)
Not willing to take part in research	21 (5.1)
Other reason for declining	11 (2.7)
Did not want to complete study questionnaires	9 (2.2)

Appendix 2 Full unit cost information for *Chapter 5*

TABLE 31 Full unit cost information

Item of resource use and associated care report form	Cost (£)	Cost description	Source
Hospital visits			
Variable – VisitType			
Outpatient visit	161.17	WF01A Non-Admitted Face-to-Face Attendance, Follow-up	NHS Reference costs 2020/2021
Ward review (not admitted)	161.17	WF01A Non-Admitted Face-to-Face Attendance, Follow-up	NHS Reference costs 2020/2021
Elective hospital admission	2358.92	LB16K Urinary Incontinence or Other Urinary Problems, without Interventions, with CC Score 0–1	NHS Reference costs 2020/2021
Emergency hospital admission	509.11	LB16K Urinary Incontinence or Other Urinary Problems, without Interventions, with CC Score 0–1	NHS Reference costs 2020/2021
Investigations			
Variable – TestType			
Invasive urodynamics	230.29	LB42A Dynamic studies of Urinary Tract (OPROC)	NHS Reference costs 2020/2021
Non-invasive urodynamics	230.29	LB42A Dynamic studies of Urinary Tract (OPROC)	NHS Reference costs 2020/2021
Cystoscopy	272.95	LB72A Diagnostic Flexible Cystoscopy, 19 years and over – Outpatient procedure Urology (OPROC)	NHS Reference costs 2020/2021
MSU test	10.18	DAPS07 Microbiology (Directly Accessed Pathology Services)	NHS Reference costs 2020/2021
Voiding assessment – catheterisation	213.28	LB18Z Attention to Suprapubic Bladder Catheter – Urology	NHS Reference costs 2020/2021
Renal ultrasound scan	64.31	RD41Z Ultrasound scan with duration of < 20 minutes, with contrast (IMAG-Outpatient), (Outpatient Ultrasound scan with duration of < 20 minutes, with contrast IMAG RD40Z £62.39, duration more than 20 minutes, with/without contrast RD42Z £68.88, RD43Z £94.26)	NHS Reference costs 2019/2020 inflated using NHSCII
CT	93.94	RD20A CT scan of one area with contrast 19 years + (IMAG-Outpatient) (CT scan of one area without contrast 19 years + (IMAG-Outpatient) RD21A £138.22)	NHS Reference costs 2019/2020 inflated using NHSCII
MRI	325.33	RD02A MRI Scan of one area with post-contract 19 years + (IMAG-Outpatient) (MRI Scan of one area without post-contract 19 years + (IMAG-Outpatient) RD01A £145.76)	NHS Reference costs 2020/2021
BoNT-A_treatment sessions[a]			
Drug costs[b]			
BoNT-A 50 unit	71.63	Average cost of 50 units Botox from all 50 units Botox listed in BNF[a]	BNF 2021
BoNT-A 100 unit	166.00	Average cost of 100 units Botox from all 100 units Botox listed in BNF[a]	BNF 2021

TABLE 31 Full unit cost information (*continued*)

Item of resource use and associated care report form	Cost (£)	Cost description	Source
BoNT-A 200 unit	268.10	Average cost of 200 units Botox from all 200 units Botox listed in BNF[a]	BNF 2021
BoNT-A 500 unit	308.00	Average cost of 500 units Botox from all 500 units Botox listed in BNF[a]	BNF 2021
Cystoscope costs			
Cystoscope + general/regional	731.84	LB72A Diagnostic Flexible Cystoscopy, 19 years and over – Day case	NHS Reference costs 2020/2021
Cystoscope + local / local plus sedation	272.95	LB72A Diagnostic Flexible Cystoscopy, 19 years and over – Outpatient procedure Urology (OPROC)	NHS Reference costs 2020/2021
Other medical care and appointments			
Absorbent pads	5.00	Absorbent pad usage as reported by women in the trial.	NHS price not available. Price based on a pack of 30 pads from online search of products.
Intermittent catheter	162.12	Intermittent catheter costs came from the NHS drug tariff for Lofric self-catheters based on expert opinion. Frequency of use was calculated as follows (based on expert opinion): • If in use at 6 months, assumed used since the first operation. • If in use at 6 months but first operation was after 6 months, assumed used from randomisation. • If in use at two time points (i.e. at 6 and 15 months) then assumed it was used the full period between the time points. • If used at 6, 15 and 24 months then it was used all the time from the operation till the 24-month FU	NHS Reference costs 2020/1
Vesicare	36.11	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
Toviaz (Festoterodine/ Zecatrin/Teraleve)	27.59	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
Tolterodine	15.10	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
Duloxetine	11.06	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
Oxybutynin	11.70	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
Trospium	14.67	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
Kentra	3.40	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
Betmiga	27.57	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
UTI antibiotic	7.98	Weighted average cost from PCA workbook January 2021[a]	NHS Business Services Authority, 2021
Clinic appointment	161.17	WF01A Non-Admitted Face-to-Face Attendance, Follow-up	NHS Reference costs 2020/2021

continued

TABLE 31 Full unit cost information (*continued*)

Item of resource use and associated care report form	Cost (£)	Cost description	Source
Phone call	119.21	WF01C Non-Admitted Non-Face-to-Face Attendance, Follow-up	NHS Reference costs 2020/2021
SNM procedures			
SNM + permanent + inpatient	9036.45	LB79Z Insertion of Neurostimulator Electrodes for Treatment of Urinary Incontinence – elective inpatient	NHS Reference costs 2020/1
SNM + permanent + day surgery unit	1614.97	LB79Z Insertion of Neurostimulator Electrodes for Treatment of Urinary Incontinence – day case	NHS Reference costs 2020/2021
SNM + permanent + main theatre unit	1614.97	LB79Z Insertion of Neurostimulator Electrodes for Treatment of Urinary Incontinence – day case	NHS Reference costs 2020/2021
SNM + not permanent + inpatient	5429.52	LB80Z Insertion of Neurostimulator for Treatment of Urinary Incontinence – elective inpatient	NHS Reference costs 2020/2021
SNM + not permanent + day surgery unit	3540.69	LB80Z Insertion of Neurostimulator for Treatment of Urinary Incontinence – day case	NHS Reference costs 2020/2021
SNM + not permanent + main theatre unit	3540.69	LB80Z Insertion of Neurostimulator for Treatment of Urinary Incontinence – day case	NHS Reference costs 2020/2021
Variable – Return to Theatre			
Lead removal	517.30	LB20G Infection or Mechanical Problems Related to Genito-Urinary Prostheses, Implants or Grafts, without Interventions, with CC Score 0–1	NHS Reference costs 2020/2021
SUI procedures			
Fascial (fascial sling)	7319.10	LB59Z Major, Open or Laparoscopic, Bladder Neck Procedures (Female)	NHS Reference costs 2020/2021
Urethral bulking agent	321.46	LB55A Minor or Intermediate, Urethra Procedures, 19 years and over – Urology – OPROC outpatient procedures	NHS Reference costs 2020/2021
Primary and community care			
GP	33.00	Surgery consultation lasting 9.22 minutes	PSSRU Unit costs of health and social care staff 2021
Practice nurse	21.00	Assume 30-minute appointment	PSSRU Unit costs of health and social care staff 2021
Physiotherapist	20.50	Assume 30-minute appointment	PSSRU Unit costs of health and social care staff 2021
Social Care	23.00	Assume 60-minute appointment as they have to travel, too.	PSSRU Unit costs of health and social care staff 2021

CT, computed tomography; MRI, magnetic resonance imaging; MSU, mid-stream urine.
a BoNT-A treatments sessions are costed as the sum of two components; drug costs plus the NHS reference cost for cystoscope (general/regional or local plus sedation).
b Costs relate to the mean price across the products that are available for each dose.

Appendix 3 Economic evaluation review, conceptual modelling and parameterisation

Introduction

The purpose of this appendix is to provide information in relation to the decision-analytic model used for the economic evaluation of urodynamics as part of the FUTURE trial. An overview is given in *Chapter 5*, but the supporting information provided here is considered too detailed for the main body of the report.

The appendix summarises the decision problem that the decision-analytic model needs to inform. The model conceptualisation is based on the decision problem and is informed by literature reviews which are reported here. Once the model structure was agreed upon, a further set of reviews was required to inform the parameterisation of the model, with these reviews also being reported here. Consequently, this appendix has the following sub-sections:

- Decision problem
- Summary of the modelling as described in the HEAP
- Review of economic evaluations of urodynamics, SNM and/or BoNT-A
- Description of our model
- Review of long-term costs and outcomes:
  - SNM
  - BoNT-A
  - Surgery for SUI.

Decision problem

The FUTURE trial relates to the care of women with refractory OAB symptoms. In essence, undertaking an urodynamics study provides additional information to clinicians about the cause of the symptoms, which in turn, is thought to allow a more appropriate choice of treatment.

The clinical pathway of the model needs to align with routine clinical practice in the UK. While a NICE Clinical Guideline (NG123) exists for OAB in women,[3] this does not accurately reflect the realities of NHS practice. The pathways adopted for FUTURE were considered to be a better representation of UK clinical practice as they were the product of detailed discussions by the recruiting sites; reassuringly, they are broadly aligned to NG123. These pathways are shown in *Report Supplementary Material 1* (see www.fundingawards.nihr.ac.uk/award/15/150/05).[75] As the cost and health consequences of different treatment pathways will be lifelong, a lifetime horizon is considered appropriate for this decision.

Summary of the modelling as described in the Health Economics Analysis Plan

While the HEAP provides a lot of details in relation to the economic evaluation, the following principles are considered to be of greatest importance to the development of the model:

- The first 24 months of the model will be based on trial results.
- A long-term decision tree model will be adapted from a pre-existing model.[52,115] Improvements to the model design/structure will be considered based on the results of literature searches.

- Persistence of treatment effect beyond the trial follow-up will be assessed using standard extrapolation methods. This will be based around model structure and data used to derive transition probabilities.
- For some parameters of interest where data were not collected in FUTURE (or longer-term estimates), the values for these will be obtained from the Goranitis *et al.* model.[115] Where necessary, these parameter values will be updated using targeted literature searches.

Review of economic evaluations of urodynamics, sacral neuromodulation and/or botulinum toxin injection A

Literature searches were undertaken of economic evaluations of urodynamics, SNM and BoNT-A. Semistructured searching was adopted using web searches of articles, and then snowballing via citation searches and reference searches.

Urodynamics

A HTA monograph examined the cost-effectiveness of urodynamics in women who have failed on first-line conservative treatment.[52] This has been published separately (Goranitis *et al.*, 2016) and offers a more focused explanation of the work.[115] The model is based around a decision tree of diagnostic performance for urodynamics versus clinical history, followed by BoNT-A, PTNS or sling as first-line treatments. SNM is a second-line treatment for non-SUI patients. The outcome of treatment is either successful or unsuccessful treatment, with the latter leading to further investigations and/or treatment. It has a 5-year time horizon and assumes that women achieving a subjective cure remain cured for the full-time horizon of the model. A maximum of three BoNT-A injections is assumed, SNM revisions, maintenance and removal are included.

Homer *et al.* (2018)[116] is an early evaluation assessing the value of a trial for invasive urodynamic testing (IUT) prior to surgery for SUI; it is based on the results of a pilot trial and formed part of a NIHR HTA project.[117] IUT costs are micro-costed and have been made available to the lead author upon request. The 6-month trial results are not extrapolated. A value-of-information analysis has been undertaken based on the 6-month trial results.

Sacral neuromodulation and botulinum toxin injection A

Leong *et al.* (2011) model SNM versus BoNT-A in patients with idiopathic OAB in the Netherlands.[59] It is a Success-Failure model based on a decision tree with Markov terminal nodes and a 5-year time horizon and a hybrid model using decision tree and Markov structures. The model uses assumptions to describe the proportion of patients at second line who get treatment or no treatment, and the failure rate for BoNT-A.

Arlandis *et al.* (2011) compared SNM, BoNT-A and continued optimised medical treatment (OMT) for patients with refractory idiopathic OAB-wet patients in Spain, with a 10-year time horizon.[118] It has a similar structure to that of Leong *et al.*,[59] although cytoplasty is available as a subsequent treatment for unsuccessful SNM or BoNT-A. Treatment outcomes by year are given, but they are not adequately sourced and so the underlying data cannot be identified. Adverse events are included; however, it is not clear whether rates of AEs are annual, or over 10 years.

Martinson *et al.* (2013) undertook a cost analysis of SNM versus PTNS using a decision-analytic model.[119] It is a hybrid model with decision tree and Markov components, with a 2-year time horizon. It is based around treatment success and failure, although initial and long-term therapy are separated out in the decision, as too are AEs. There are no subsequent lines of therapy.

The study by Autiero *et al.* (2015)[120] is the same model as Arlandis *et al.*,[118] but the paper has been retracted. The retraction (2018) states that:

> *Whilst the authors are confident that the model inputs (literature, unit cost sources and clinical expert advice) were valid at the time of the analysis, there are integral errors in the structure of the model, which result in treatment costs*

and utility values being applied incorrectly to the patient population in both treatment arms. The principal source of the errors has been found to be the original model initially developed for Spain (Arlandis et al. Value Health. 2011 Mar-Apr;14(2):219–28), which was adapted for the UK for this analysis.

As such, the underlying data and conceptual structure are still of interest. The population is reported as medically refractory idiopathic OAB (wet) patients. The treatment success rates are identical to those of Arlandis *et al.*[118] However, the underlying sources are clearly referenced. BoNT-A success rates are based on single injection studies, with an assumption of annual loss of effect over 10 years.

Hassona and Sadri (2015) model SNM, BonT-A, OMT and cytoplasty in refractory OAB in Canada.[121] Outcomes are classified as Success or Failure. They use a 10-year horizon and the same basic model as Arlandis[118] and Autiero,[120] although SNM is modelled as two discrete stages: test and permanent. Annual failure rates are given for SNM, BoNT-A and OMT, but these are not sourced. They are, however, identical to those of Arlandis[118] and Autiero.[120] The work is generally quite poorly reported.

Murray *et al.* (2019) model SNM, BoNT-A, PTNS, anticholinergic medications, mirabegron and best supportive care for the management of refractory OAB in the USA.[122] A 10-year time horizon is used. They use a five-state Markov model, with four being defined by the frequency of UI episodes per day (0, > 0 to ≤ 2, > 2 to < 5, ≥ 5), and the remaining state being death. Transition probabilities for BoNT-A were based on pooled patient-level trial data, with transitions beyond 1 year being approximated by the trial data for patients who remained on BoNT-A for more than 12 months. Transitions for other treatments could not be directly estimated as patient-level data were not available to the authors and so assumptions were made to generate these from the data available. All patients who discontinued therapy switched to best supportive care.

Conclusions

- Hybrid models are most commonly used, which mix features of decision trees and Markov processes. The decision tree component is used to describe treatment pathways, while the Markov component is used to describe long-term effects once treatment sequences have ended.
- One 'pure' Markov model was found. However, due to the lack of available data with which to populate the transitions, it is heavily based on the use of assumptions. Consequently, the greater granularity of response that it provides is seriously diminished. The study also ignores lines of therapy beyond the initial treatment choice.
- No studies use a lifetime horizon; 10 years is the longest.
- Success rates for treatment used in these models are based on heterogeneous studies; patient populations are not always clearly defined, definitions of success vary and the prior use of urodynamics to guide therapy is difficult to identify (but generally thought to be unlikely).

Description of our model

The Goranitis *et al.* model[115] is the most relevant to an evaluation of urodynamics and has many features in common with most of the other models that we have reviewed (e.g. a decision tree structure to describe treatment sequences and use of 'success/failure' to describe treatment outcomes). However, its detailed description of urodynamics diagnoses and treatments is not necessary given the evidence base made available by FUTURE. Consequently, a simpler structure that is more akin to the other studies reviewed is considered more appropriate.

It was felt that a simple structure that was clearly linked to the results of FUTURE was important, and this was possible by using its 24-month outputs as the first inputs to the model, together with the final treatment allocations and utilities. This was undertaken using a decision tree to describe trial results and final treatment allocations, with a Markov formulation beyond that point which extrapolated treatment allocations, costs and outcomes beyond that point. Our model is shown in *Appendix 3*, *Figure 16*.

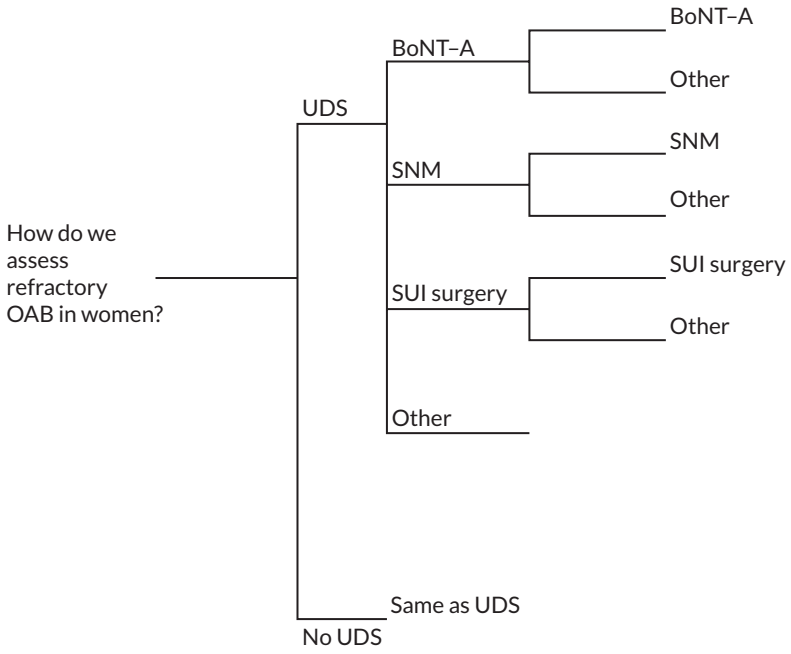

FIGURE 16 Model structure used in FUTURE. UDS, urodynamics.The nodes immediately to the right of 'UDS' and 'No UDS' are Markov nodes; descriptors on the far right represent transitions to the relevant Markov node. Death is included in the model but is excluded from this figure for simplicity.

In summary, treatment success leads to continued treatment, while treatment failure leads to 'other care' (which consists of various treatments and further clinical assessments as observed in FUTURE). Long-term success rates are based on literature estimates, which are reviewed in the next section.

Modelling of more complex pathways that involve all available treatments and possible sequences was considered to be beyond the scope of this study. For example, treatment for SUI represents one point in a single pathway within FUTURE. However, on closer inspection it is clear that this treatment is, in fact, a complex decision problem in its own right; a NIHR-funded modelling study of surgical treatments for SUI examined nine different treatments.[123]

Review of long-term costs and outcomes

For evidence on the long-term outcomes associated with urodynamics and subsequent treatment, a systematic review of urodynamics was examined (Lor *et al.*, 2020).[124] The longest follow-up from the systematic review is 36 months, but with small sample sizes ($n < 100$); a 49-month study is reported only as a conference abstract. The highest-quality study (Nager *et al.*, 2012) has a 12-month follow-up with 315 patients;[37] this is shorter than FUTURE and so has not been used to inform our modelling. Consequently, literature reviews were undertaken relating to the long-term outcomes of the treatments indicated by urodynamics, which are described below.

The approach of using long-term outcomes for individual treatments is problematic in two ways. First, the outcomes are not contingent on the method of diagnosis, that is, whether the woman is prescribed treatment based on urodynamics or otherwise. This is problematic as the use of urodynamics is predicated on its ability to help inform more appropriate and, as such, more effective treatment. Second, the populations reported in the literature may not match those in FUTURE and, as such, the long-term outcomes may not align with those observed in FUTURE. We attempt to mitigate the effects of these two issues by adjusting the long-term outcomes using success rates observed in FUTURE. So, for example, if FUTURE give a 60% success rate for a particular treatment at 12 months, but the literature reports

a long-term cohort with a 75% success rate at 12 months, reducing to 50% at 60 months, the observed 12-month value of 60% will be used in the model, together with long-term outcomes adjusted such that the estimated 60-month success rate is 60% × (50/75) = 40%.

It is important to note that all the success rates identified below are unadjusted, with the adjustment being applied in the model (and, as such, contingent on the success rates observed in the trial).

Sacral neuromodulation

Literature

The 10-year model used in the Arlandis *et al.*, Autiero *et al.* and Hassouna and Sadri papers, all of which have links with Medtronic, appear to use five studies to generate long-term SNM success rates.[118,120,121] The success rates that they produce from these studies are shown in *Appendix 3*, *Table 32*. Note that the figures in *Appendix 3*, *Table 32* also include an element of expert judgement; the plateau at 75% is thought to be based on expert opinion.

Also of interest from the long-term modelling are the long-term costs associated with SNM. The two main aspects of this, in addition to standard clinical follow-up, are reoperations and explantations. The parameters within the models are summarised in *Appendix 3*, *Table 33*. However, these are generally reported less clearly, with variability in relation to what constitutes a 'reoperation'.

TABLE 32 Success rates for SNM used in the Arlandis *et al.*, Autiero *et al.* and Hassouna and Sadri papers

Time	Success rates (%)
1 year	90
2 years	86
3 years	82
4 years	78
5 years	75
7 years	75
10 years	75

TABLE 33 Reoperation and explantation rates used in economic evaluations

Lead author	Reoperation	Explantation
Arlandis[118] and Hassouna[121]	8% (Kessler, which includes explantation)	Included in the reoperation rate
Autiero[120]	15% (expert opinion)	Not included
Goranitis[115]	Probability of revision before 2 years, 0.090, and 0.330 from 2 to 5 years	Probability of 0.107 at 5 years
Leong[59]	16% over mean follow-up of 16 months, plus battery replacement every 7 years	7.5% explantation over mean follow-up of 16 months

Note
Other studies do not include or report data relating to reoperations or removals.

The figures in *Appendix 3*, *Table 32* and *Appendix 3*, *Table 33* are potentially problematic in a number of ways. First, they are quite old and could potentially reflect outcomes from outdated devices/procedures. Second, even if relevant for some outcomes, they represent only a partial picture of the entire evidence base; we have identified eight other studies published after those in these models. Thirdly, all three models are directly linked to Medtronic, who is a manufacturer of SNM devices. Consequently, we have summarised the eight more recent studies in *Appendix 3*, *Table 34*.

Note that although these papers are more recent, some include old cohorts that include previous techniques/devices. Also, there are subtle differences in diagnoses, mean age of population cohorts and study design (e.g. prospective/retrospective and, potentially, definitions of success). These studies seem to suggest that the success rates in

TABLE 34 Summary of studies published after the Medtronic model

Author (year), country	Population	Sample size	Success rates (definition)	Definition of success	Other data
Siegel (2018), USA[125]	OAB and one medication failure	340 test, 272 implant	5 years = 67%	Urinary urge incontinence or urgency-frequency response of 50% or greater improvement in average leaks or voids per day	33.5% surgical reintervention rate at 5 years. 19.1% explantation rate at 5 years.
Peeters (2014), Belgium[126]	Various dysfunctions, OAB reported separately	382 test, 217 implant	4 years = 70% UI and 68% UFS Mean 46.88 months	≥ 50% improvement in any of the primary voiding diary variables	41% surgical reintervention rate at 4 years. 18% explantation rate at 4 years.
Marcelissen (2010), Netherlands[127]	Refractory OAB or urinary retention	92 test, 64 implant	4 years = 64% Mean 53 months	Clinical success was defined as more than 50% improvement in at least 1 voiding diary parameters	Some data reported but very difficult to understand
Amundsen (2018), USA[128]	Refractory UUI	169 test, 139 implant	Not reported. Mean changes in symptoms/QoL reported at 2 years	50% reduction in UUI episodes. This was a trial of SNM versus BTX. Same success criterion was used for both	3% required revision. Explantation rate 8.6% Lower revision rate attributed to newer devices and leads
Kessler (2006), Switzerland[129]	Refractory Lower Urinary Tract Dysfunction (UI, UR, CPPS)	209 test, 91 implant	2 years =70% Median 25 months	Unclear. Probably more than 50% in bladder/pain diary variables	7% required revision. 1% explantation.
Kaaki (2020), USA[130]	Refractory OAB (failure of two medications)	55 test, 66 implant	3 years = 74.5% Median 32 months	> = 50% improvement in any clinical parameter	18.2% require revision surgery after a median duration of 21.9 months; 27.3% required explantation after a median duration of 24 months
Ismail (2017), France[131]	Refractory idiopathic OAB	34 implants	10 years = 63% Median 9.7 years	Improvement 50% of any symptom	22 revision surgeries in 15 (47%) patients, with mean time to first surgery of 6.2 years. Explantation rate of 6.3%
Al-zahrani (2011)[132]	UUI, BPS and IUR (some results reported separately)	196 test, 96 implant (UUI figures available)	4 years = 84.8% UUI Median 50.7 months	Good or very good outcome on a 5-point Global Response Assessment Scale	For UUI, 32% revision rate, with mean time revision of 23.7 months from implant. Explantation rate of 14.7%, with mean explantation time of 41.5 months from implant.

BPS, bladder pain syndrome; BTX, botulinum toxin injection A; CPPS, chronic pelvic pain syndrome; IVR, idiopathic urinary retention; UR, urinary retention.

Appendix 3, *Table 32* are optimistic, especially for the population that is most closely aligned to that in FUTURE; Kaaki and Gupta (2020)[130] and Ismail *et al.* (2017)[131] appear to be the most relevant populations for our work.

Model parameters for SNM

Based on this review, we propose that rates for success, surgical revision and removal are as given in *Appendix 3*, *Table 35*.

For the probabilistic sensitivity analysis (PSA), uncertainty relating to these parameters was captured by making reference to the samples sizes on which they are based and then incorporating these within a binomial distribution. Success rates for years 1–3 are based on Kaaki and Gupta (2020), with the rate being in relation to 55 patients.[130] For year 10, the rate is based on Ismail *et al.* (2017), which is 20 out of 32 patients.[131] The intervening years are interpolated and use the smaller sample size of 32.

Botulinum toxin injection A

Literature

The Medtronic model uses two studies of one-injection trials to generate a success rate at 1 year, then applies an assumed 7.5% discontinuation rate to generate success rates up to 10 years (Autiero *et al.* 2015).[120] Note, however, that they have misapplied this assumption when calculating the 7- and 10-year success rates (which should be 50% and 40%, rather than 54% and 50%).

Subsequent to this, a systematic review was undertaken by two NIHR Biomedical Research Centres which identified 13 studies (12 English-language) of medium-term treatment outcomes, with a maximum follow-up of around 7 years (although the longest reported mean follow-up is 3.2 years).[133] All publications citing this article have been identified and no additional source studies of medium- or long-term outcomes were evident; a systematic review and network meta-analysis of treatments for OAB was identified, but this was limited to RCTs and 12-week outcomes, which together with population heterogeneity render it irrelevant for our purposes.[134]

TABLE 35 Model parameters for SNM

Time	Success rates (cumulative %)[a]	Surgical revision (% per annum)[b]	Removal (cumulative %)[c]
1 year	77.1	8.9	0
2 years	75.6	8.9	26
3 years	74	8.9	26
4 years	72.4	8.9	27.6
5 years	70.9	8.9	29.1
6 years	69.3	8.9	30.7
7 years	67.7	8.9	32.3
8 years	66.1	8.9	33.9
9 years	64.6	8.9	35.4
10 years	63	8.9	37

a Kaaki and Gupta (2020) used for year 3, Ismail *et al.* (2017) used for 10 years, with straight line interpolation between those two points. Years 1 and 2 estimated through interpolate from year 3 using the same annual change estimated for years 3–10.
b Revision rates appear broadly linear with time from Al-zahrani *et al.* (2011) and Ismail *et al.* (2017), therefore median time to revision equals mean time to revision; 22.3 months used (average of Kaaki (2020) and Al-zhrani (2011), as Ismail (2017) is an outlier). 8.9% derived using backward calculation of fixed rate over 4 years (to reflect Kaaki and Al-zhrani follow-up periods).
c Removal rates are approximately 1 minus success rates in both studies. However, removals within 1 year are considered unlikely.

Unfortunately, the review by Eldred-Evans and Sahai (2017) reports very little of the outcomes for each study; its focus appears to be number of injections and their associated interval.[133] Also, the outcome measures that are summarised suggest that 'success rates' are not commonly reported; proportion remaining on treatment (or retreatment rates) is used as the measure of success. The three largest studies are summarised in *Appendix 3*, *Table 36*.

Mohee *et al.* (2013) also highlight those treatments undertaken after discontinuation, with these including SNM, ileocystoplasty, ileal conduit diversion, and reversion to medical management.[57] These data, together with the Brazzelli *et al.* review of treatments for SUI,[123] highlight the complexity of trying to capture all possible treatment pathways beyond the initial treatment for refractory OAB.

Adverse events are reported in all studies; however, these are all minor (e.g. UTIs). Dose reductions occur in some patients; however, these are not reported clearly within the studies.

Model parameters for botulinum toxin injection A

Based on this review, Mohee *et al.* (2013)[57] appears to be the most appropriate source of data due to it being UK-based, having the longest follow-up and having a patient population that is close to that in FUTURE. Data were extracted from the Kaplan–Meier plot shown in the paper using WebplotDigitizer (https://automeris.io/WebPlotDigitizer/). The resultant annual success rates are shown in *Appendix 3*, *Table 37*. The 5-year estimate is used as the success rate for subsequent years as the associated Kaplan–Meier curve plateaus at this level.

As BoNT-A typically requires multiple treatments, time on treatment needs to be combined with a mean time to retreatment in order that costs can be calculated. Again, Mohee *et al.* (2013)[57] is used, and their figure of 8.2 months between treatments is adopted in our model.

TABLE 36 Summary of largest studies identified in the Eldred-Evans review

Author (year), country	Population	Sample size, follow-up	Outcomes	Relevant to model
Nitti (2016), USA and Europe[135]	OAB, 90% female	839, median 3.2 years	UI episodes per day, I-QOL scores, and AEs	Discontinuations and time to retreatment
Mohee (2013), UK[57]	Refractory OAB with DO confirmed by UDS, 69% female	228, with 137 followed for ≥ 36 months, 80 ≥ 60 months	Continuation, treatment efficacy and AEs (limited reporting)	Discontinuations and limited retreatment data
Dowson (2012), UK[136]	Refractory OAB (failure on a least one drug) and UDS, 76% female	100, length of follow-up not reported	Numbers of injections, symptoms, and AEs	Inter-injection interval of 322 days is reported; full data only available in figures.

UDS, urodynamics.

TABLE 37 Botulinum toxin injection A annual success rates

Time	% remaining on treatment
1 year	64
2 years	51
3 years	43
4 years	38
5 years	38
5 + years	38

For the PSA, uncertainty relating to these parameters was captured by making reference to the samples sizes on which they are based and then incorporating these within a binomial distribution. The success rates are taken from Mohee *et al.* (2013),[57] which is based on a cohort of 137 patients.

Surgery for stress urinary incontinence

Literature

A recent systematic review of long-term outcomes of treatment for SUI was identified (Brazzelli *et al.* 2019).[123] In their associated economic model, long-term cure rates were estimated for mid-urethral sling using a Weibull survival model. The effectiveness of other surgical treatments was estimated by using the results of a network meta-analysis shown in *Appendix 3*, *Table 38*.

Model parameters for stress urinary incontinence

Using a Weibull model (with scale and shape parameters of 0.174 and 0.4585, respectively) fitted to Brazelli's mid-urethral sling cure rates in *Appendix 3*, *Table 38* produces the estimates in *Appendix 3*, *Table 39*. Further reductions beyond 10 years are incorporated in the model using the full Weibull function.

For the PSA, uncertainty capturing both the underlying evidence (for which Brazelli undertakes a meta-analysis) and the curve fitting (for which Brazelli uses three curves from different sets of evidence) is captured. To do this, we identified the 5-year success rates for their most optimistic and least pessimistic models (75% and 50%, respectively), and calibrated the standard errors associated with the baseline scale and shape parameters to reproduce those.

TABLE 38 Mid-urethral sling success rates taken from Brazelli *et al.* (2019)

Years	Median	95% CI	Number of studies	Number of participants
1	0.841	0.214 to 0.990	44	2882
2	0.784	0.454 to 0.941	6	315

TABLE 39 Cure rates for mid-urethral sling as estimated by Brazzelli *et al.*

Time	Success rates (%)
1 year	84.0
2 years	78.4
3 years	74.3
4 years	71.1
5 years	68.4
7 years	63.9
10 years	58.8

Other model parameters for the Female Urgency, Trial of Urodynamics as Routine Evaluations cost-effectiveness model

In addition to the transition probabilities for BoNT-A, SNM and surgery described above, the following additional parameters were required, all of which were sourced from the FUTURE trial (see *Appendix 3*, *Table 40*). In short, costs

TABLE 40 Model parameters derived from FUTURE

Parameter		Time point(s)	Mean	Distribution	Source
Costs at 24 months (discounted)					
UDS + CCA		Up to 24 months[a]	3907.33	Normal (SE = 466.02)	FUTURE
CCA		Up to 24 months[a]	3444.78	Normal (SE = 449.79)	FUTURE
QALYs at 24 months (discounted)					
UDS + CCA		Up to 24 months[a]	1.315	Normal (SE = 0.057)	FUTURE
CCA		Up to 24 months[a]	1.304	Normal (SE = 0.056)	FUTURE
Last treatment at 24 months (%)					
UDS + CCA	BoNT-A	At 24 months	49.27	Binomial, 271/550	FUTURE
	SNM	At 24 months	1.82	Binomial, 10/550	FUTURE
	SUI surgery	At 24 months	2.55	Binomial, 14/550	FUTURE
	Other	At 24 months	46.36	Binomial, 255/550	FUTURE
CCA	BoNT-A	At 24 months	61.93	Binomial, 340/549	FUTURE
	SNM	At 24 months	1.09	Binomial, 6/549	FUTURE
	SUI surgery	At 24 months	0.73	Binomial, 4/549	FUTURE
	Other	At 24 months	36.25	Binomial, 199/549	FUTURE
Utilities at 24 months for:					
BoNT-A		After 24 months[a]	0.632	Normal (SE = 0.041)	FUTURE
SNM		After 24 months[a]	0.599	Normal (SE = 0.036)	FUTURE
SUI surgery		After 24 months[a]	0.643	Normal (SE = 0.045)	FUTURE
Other		After 24 months[a]	0.612	Normal (SE = 0.040)	FUTURE
Unit/annual costs (undiscounted)					
BoNT-A (applied to re-treatment)[b]		After 24 months	£463.75	Deterministic	FUTURE
SNM (applied to revisions)[c]		After 24 months	£1614.97	Deterministic	FUTURE
SUI surgery		After 24 months	0	Deterministic	Assumption
Other[d]		After 24 months[a]	£1723.31	Normal (SE = 252.79)	FUTURE[3]

UDS, urodynamics.
a Adjusted using age and gender population norms with the base-case model.
b BoNT-A cost is derived from the Healthcare Resource Group LB72A Diagnostic Flexible Cystoscopy, 19 years and over – Outpatient procedure Urology (OPROC) (see Appendix 2), plus the cost of the mean Botox dose (120 iu). Re-treatment happens every 8.2 months.
c SMN revision cost is based on Healthcare Resource Group LB79Z Insertion of Neurostimulator Electrodes for Treatment of UI – day case. Removal is also applied upon transition to 'Other care' and is £517.30 LB20G Infection or Mechanical Problems Related to Genito-Urinary Prostheses, Implants or Grafts, without Interventions, with CC Score 0–1 (see *Appendix 2*).
d Annual cost associated with the 'other' health state is estimated as the 24-month mean cost for those who did not receive BoNT-A, SNM and SUI from a model with costs associated with the intervention removed, divided by 2 to obtain an annual cost.

and QALYs up to 24 months are taken from the within-trial analysis, with the proportion of patients currently on each treatment also coming from FUTURE. Ongoing costs for the three defined treatments – BoNT-A, SNM and SUI – relate only to those treatments (i.e. BoNT-A sessions, removals, revisions, and for SUI treatments there are zero ongoing costs). Ongoing costs for 'Other' were derived from the trial (see table for details).

For the subgroup analysis of women with an initial diagnosis of MUI, a different set of parameters was derived from the trial relating to that group of patients. These are shown in *Appendix 3*, *Table 41*.

TABLE 41 Model parameters for the MUI subgroup derived from FUTURE

Parameter		Time point(s)	Mean	Distribution	Source
Costs at 24 months (discounted)					
UDS + CCA		Up to 24 months	3958.75	Normal (SE = 525.98)	FUTURE
CCA		Up to 24 months	3505.61	Normal (SE = 501.84)	FUTURE
QALYs at 24 months (discounted)					
UDS + CCA		Up to 24 months	1.369	Normal (SE = 0.063)	FUTURE
CCA		Up to 24 months	1.316	Normal (SE = 0.060)	FUTURE
Last treatment at 24 months (%)					
UDS + CCA	BoNT-A	At 24 months	43.32	Binomial, 81/187	FUTURE
	SNM	At 24 months	2.67	Binomial, 5/187	FUTURE
	SUI surgery	At 24 months	3.74	Binomial, 7/187	FUTURE
	Other	At 24 months	50.27	Binomial, 94/187	FUTURE
CCA	BoNT-A	At 24 months	59.78	Binomial, 110/184	FUTURE
	SNM	At 24 months	0.54	Binomial, 1/184	FUTURE
	SUI surgery	At 24 months	2.17	Binomial, 4/184	FUTURE
	Other	At 24 months	37.50	Binomial, 69/184	FUTURE
Utilities at 24 months for:					
	BoNT-A	After 24 months	0.626	Normal (SE = 0.065)	FUTURE
	SNM	After 24 months	0.569	Normal (SE = 0.065)	FUTURE
	SUI surgery	After 24 months	0.700	Normal (SE = 0.073)	FUTURE
	Other	After 24 months	0.637	Normal (SE = 0.065)	FUTURE
Unit/Annual costs (undiscounted)					
BoNT-A (applied to re-treatment)		After 24 months	£463.75	Deterministic	FUTURE
SNM (applied to revisions)		After 24 months	£1614.97	Deterministic	FUTURE
SUI surgery		After 24 months	0	Deterministic	Assumption
Other		After 24 months	£1765.341	Normal (SE = 275.14)	FUTURE

Appendix 4 Observed quality-adjusted life-year loss associated with urodynamics procedure

Introduction

An exploratory analysis was undertaken to assess the QALY loss related to urodynamics (e.g. anxiety and discomfort) by estimating the degree to which EQ-5D-5L values at 6 months post randomisation were affected by time since urodynamic testing.

Methods

This analysis took the form of a regression using the difference between post-urodynamics and pre-urodynamics utility as the dependent variable, and time since urodynamics, its squared term, and other covariates as the independent variables. If the hypothesis of disutility associated with the urodynamics treatment were to hold, we would expect a negative relationship between the change in utility and the time since the post-urodynamic measure was taken. Participants were limited to those in the urodynamics arms of the trial, and those who had completed a post-urodynamic EQ-5D-5L prior to any subsequent treatment of investigation.

Results

Two-hundred and fifty-seven pairs of observations were available (see *Appendix 4*, *Figure 17*). The results indicated no statistically significant relationship, indicating no evidence to suggest that a utility decrement exists in the trial data, and therefore no adjustment will be made for a utility decrement in our analyses (see *Appendix 4*, *Table 42*).

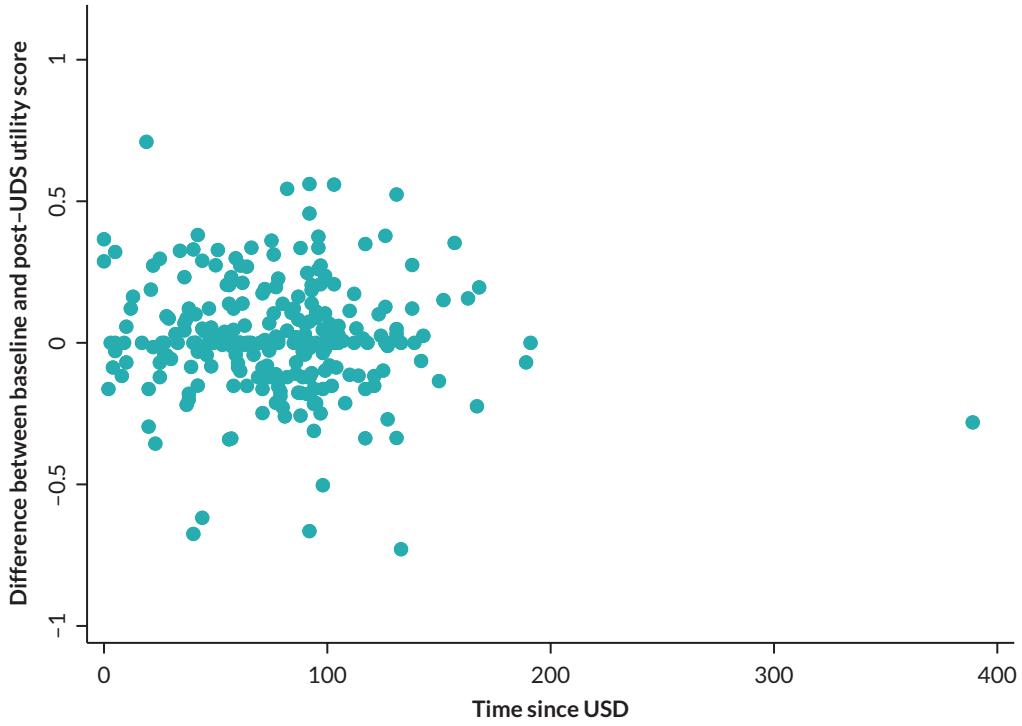

FIGURE 17 Differences in EQ-5D-5L scores between pre- and post-urodynamics as a function of intervening time. UDS, urodynamics.

Discussion

The analysis suggests that there is no observable difference in EQ-5D-5L scores relating to the administration of urodynamics testing. However, there are two clear limitations to this analysis. First, the data used are dominated by observations with differences in time between the pre and post data points that are greater than the period of time that a QALY loss would be expected. As such, any effect is 'diluted' by these observations. This could be resolved by identifying a time period beyond which an effect is considered implausible, then re-estimating the relationship. However, the choice of time period was considered to be extremely subjective. Second, the validity of the EQ-5D-5L for this purpose – the identification of small, transient changes in HRQoL – is unknown. It has been criticised for being insensitive in other conditions, and we are doubtful as to its ability to quantify any changes in this specific situation. We feel that this problem can only be satisfactorily resolved by undertaking a separate utility elicitation exercise based on descriptions generated from patient interviews. Such 'vignette' or 'direct' valuation studies tend to generate values that are more sensitive to small differences in health states; however, this may be partly due to the focusing effects of basing a valuation around a detailed description of a single event or health state.

A completely different approach to the estimation of a QALY loss related to urodynamics is to incorporate the effects of the procedure qualitatively into a decision about the provision of urodynamics in this patient population. Given the problems associated with identifying a valid utility instrument and the problems (and cost) with developing vignettes, incorporating those effects qualitatively is perhaps the best approach.

Conclusion

In an exploratory analysis of the trial data, we didn't find any robust evidence of a short-term impact on HRQoL of the urodynamics procedure on women using the EQ-5D-5L. The study analysis is limited by problems with identifying a plausible length of any effect and the validity of the EQ-5D-5L. While other approaches to quantifying any effect are possible, incorporating them into a funding decision is probably best done qualitatively.

TABLE 42 STATA output of the exploratory analysis of urodynamics impact on EQ-5D-5L scores

reg utility_diff age min_time time_squ UrinarySymtomsInterfere					
Source	**SS**	**df**	**MS**	**Number of obs = 258**	
				$F(4, 253) = 0.87$	
Model	0.138859395	4	0.034714849	Prob > F = 0.4813	
Residual	10.0722242	253	0.039811163	R^2 = 0.0136	
				Adj R^2 = −0.0020	
Total	10.2110836	257	0.039731843	Root MSE = 0.19953	
Utility_diff	Coefficient	SE	t	p > I t I	(95% CI)
Age	−0.0007753	0.0009205	−0.84	0.400	−0.0025881 to 0.0010375
min_time	−9.95e-06	0.0005901	−0.02	0.987	−0.0011722 to 0.0011523
time_squ	−1.60e-06	2.25e-06	−0.71	0.479	−6.04e-06 to 2.84e-06
UrinarySymptomsInterfere_bl	0.0011819	0.0015269	0.77	0.440	−0.0018252 to 0.004189
_cons	0.066827	0.0707517	0.94	0.346	−0.0725103 to 0.2061644

Appendix 5 Supplementary interview findings to *Chapter 6*

Clinician participant supplementary interview findings

So, we follow the NICE guidelines, it is to start, after a history and examination excluding any other similar condition which may produce similar symptoms, we start those patients with anti-muscarinic, you know the tablets, we've got very clear guidelines here. Failing that we usually proceed to urodynamic study before we discuss with the patient further invasive treatment.

07

Yes, I do wonder sometimes if I'm not unfair with not offering alternatives, but I think I certainly push the Botox more, also because I know that my colleagues who do the sacral nerve stimulation would certainly recommend that first.

03

We offer them sacral neuromodulation and Botox and tibial nerve stimulation as well.

02

If I think they're not going to be able to self-catheterise then I will direct them away from Botox.

01

I mean the problem with the bladder diary is it relies on the patient, it's a bit subjective isn't it so some patients will want to impress you with their bladder diary because they think that's how they're going to get the treatment.

01

I always believe the patient's assessment should be comprehensive. Comprehensive in the sense that we should always go back to point zero, when a person comes to the uro-gynae clinic.

08

Urodynamics is an objective way of assessing is this the true picture in a way, and most of the time it is but sometimes you get a surprise that actually that doesn't tally with what you've told me on the bladder diary so, yes.

01

There are times when obviously people with very clear-cut symptoms don't have urodynamics that you would expect but it's nice to see that they do have overactivity and that they don't have any other issues in terms of filling or emptying.

04

To be honest, we just follow guidelines.

07

It doesn't affect what we offer but our patients, a lot of patients are not keen to travel … so the clinician's preferences don't really influence the patient's decision, but the geographical location of the service affects patient's choice.

08

I think other places I think it's underutilised as a treatment and other places don't offer it to patients who deserve it or need it because it's not available and there's that reluctance to refer on.

01

There are many options now, what works for someone may not work for the other, so you have to offer all the options to the patient, I mean unless there are contraindications, we do give it completely all because the patient has to be informed and it is their decision.

07

A factor that we keep in mind is the age, so more or less, me personally I find more likely to recommend sacral nerve stimulation to somebody who is younger because if you start injecting Botox at the age of 25 or 26 you're feeling a bit more uncomfortable in a way, because they will need to have the treatment probably for the next 40/50 years which is not very convenient for them, while if they've got the sacral nerve stimulation and it's successful then they'll have more long-lasting result without needing to have repeat injections.

05

Obviously there are clinical factors that we keep in mind so more or less a patient with coexisting voiding difficulties usually they are not very good candidates for Botox so this kind of patient usually we encourage them to have nerve stimulation rather than Botox.

05

When they arrive to the clinic they are scared.

01

They are afraid of catheterisation or being assaulted or something like this.

07

When you sit them down and talk to them and explain to them and after you ask them how are you doing? they say it's [urodynamics] actually not as bad.

01

Obviously you are avoiding an invasive test, it's the cost, the inconvenience to the patient, you know the potential infection they are getting from urodynamics, so yes there are multiple advantages.

05

I suppose in the future if FUTURE shows that urodynamics is not necessary then I would be happy to live with offering one round of Botox and if it works then continue with that without urodynamics or offering a temporary stimulation and if it works then yes implant on the patient that's offered temporary stimulation, if it doesn't then go back into urodynamics.

01

I'm seeing patients back who are equally delighted whether they have or haven't had it. And a couple of patients where it's not been quite so effective or a couple of patients where they've ended up being catheterised, although we didn't intentionally set out for that to happen.

03

It's [urodynamics] helpful, it's informative but it's not a deal breaker for me.

03

Patient participant pre-randomisation supplementary interview findings

My symptoms got worse after I had my first daughter.

P12

Well normally I would go to the gym and stuff, but I feel that I can't go to a gym unless I'm quite close to the toilets.

P15

I hardly drink anything before I go, so I'm not drinking enough. And really that's the impact it's having on my life right now.

P23

So basically, last year I was working full time and actually because of these issues … I had to take about 3 absences in say 5 months of working at my job and they literally fired me for that.

P11

You kind of feel less attractive and everything as well. You just feel dirty all the time.

P13

I've been given quite a lot of tablets, at the moment I'm on two lots, they're just not working at all. I take two at bedtime and no I'm still up. The first ones I first got they worked for a wee while but then no they just stopped working.

P02

I'd try anything, I just want something that works …. I'm just going with what the doctors are saying actually … we just go with what they say and the leaflets they gave me.

P21

I think that's the only thing that would put me off is the travelling.

P03

I totally understand if it does take a while because I mean I know these things, you know, at the moment there's a lot of this, it's a big issue. So, I can understand the long waiting lists.

P08

Times are irrelevant I'm retired so waiting times I think for anything are always a long wait aren't they so I just have to put up with that, can't do much about that.

P25

You know I want to have my life back what I had before.

P21

Just not needing the toilet every two minutes after having a drink …. Not needing to wear pads all the time because that drives me nuts.

P07

To get a good night's sleep. A good nights' sleep because the other few weeks ago I had to fill a questionnaire in about how many times I was going, about every half an hour like that you know. I said I just want a nights' sleep I said I only used to get up about once a night.

P21

I'm open minded. I just want a solution.

P16

I don't know I think fear of the unknown, I think it's because I have a lot of trouble and a lot of pain in that area and so on, am I going to make things worse? How am I going to actually cope with it? What happens if it doesn't work? Then they tell me it can over work and you can't do at all and that to me is going to be even worse.

P14

Patient participant post-randomisation supplementary interview findings

I have had urodynamics done many many years ago as well. Because, I had two big operations many years ago. So, I've been every time I go to the urodynamics, I usually have something done there. So, it's something I've been used to over my lifetime.

P31

My thoughts were positive because if the medication wasn't working, I was keen to try anything that might work or at least investigate what was going on, so I had no negative thoughts about it at all

P35

Perspectives on Botox after treatment

When he spoke to me about it, I started laughing because my daughter, my youngest daughter, had just opened her own business. And she's done all this training stuff. And she started doing Botox in people's faces and everything.

P28

I just feel that if it hasn't worked the first time, then why should it work a second? And unless they say to me well, with more filler as it were, it may help. But I don't know.

P32

I think it's more frustrating [that I have to attend the hospital specifically] because I know I'm going to have this every single year now it's such a quick procedure as well just for the sake of maybe half an hour, an hour appointment at hospital every year for something.

P11

But I think overall I'm happy because the Botox has actually, I have noticed a difference in terms of my overactivity.

P11

Perspectives on self-catheterisation

I felt OK. I'm willing to try anything to get rid of this. I'm willing to try anything.

P28

I'm not a big body person, I don't like down there and messing about but if I need to do it, I'll do it.

P29

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HSDR
HTA
PGfAR
PHR

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