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

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Summary

Background Overactive bladder is a common problem affecting women worldwide, with a negative effect on their social and professional lives. Before considering invasive treatments, guidelines recommend urodynamics to identify detrusor overactivity. However, the clinical-effectiveness and cost-effectiveness of urodynamics has never been robustly assessed in this cohort of women. We aimed to compare the clinical-effectiveness and cost-effectiveness of urodynamics plus comprehensive clinical assessment (CCA) versus CCA only in the management of women with refractory overactive bladder symptoms.

Methods We did a multicentre, superiority, parallel, open-label, randomised controlled trial in 63 UK hospitals. Women aged 18 years or older with refractory overactive bladder or urgency predominant mixed urinary incontinence, with failed conservative management and being considered for invasive treatment, were randomly assigned (1:1) to urodynamics plus CCA versus CCA only. Assignment used an internet-based application with stratified random permuted blocks and site and baseline diagnosis as stratum. Primary outcome was participant-reported success at the last follow-up timepoint, measured by the Patient Global Impression of Improvement at 15 months after randomisation. Primary economic outcome was incremental cost per quality-adjusted life-year (QALY) gained modelled over the participants lifetime. Analysis was based on the intention-to-treat principle. This study is registered with ISRCTN registry (ISRCTN63268739).

Findings Between Nov 6, 2017, and March 1, 2021, 1099 participants were randomly assigned to urodynamics plus CCA (n=550) or CCA only (n=549). At the final follow-up timepoint, participant-reported success rates of "very much improved" and "much improved" were not superior in the urodynamics plus CCA group (117 [23·6%] of 496) versus the CCA-only group (114 [22·7%] of 503; adjusted odds ratio 1·12 [95% CI 0·73–1·74]; p=0·60). Serious adverse events were low and similar between groups. Incremental cost-effectiveness ratio was £42 643 per QALY gained. The cost-effectiveness acceptability curve showed urodynamics had a 34% probability of being cost-effective at a willingness-to-pay threshold of £20 000 per QALY gained, which reduced further when extrapolated over the patient's lifetime.

Interpretation In women with refractory overactive bladder or urgency predominant mixed urinary incontinence, the participant-reported success in the urodynamics plus CCA group was not superior to the CCA-only group, and urodynamics was not cost-effective at the £20 000 per QALY gained threshold.

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Introduction

Overactive bladder affects 12–14% of women in the UK. The condition has a negative effect on women's social, physical, and psychological wellbeing, and negative effects on working women's productivity. In severe cases, many women report avoiding employment, 60% report avoiding leaving home, and 50% reporting avoiding sexual activity.[1–7]

Initial treatments for overactive bladder include lifestyle modifications, bladder retraining, pelvic floor muscle training, and pharmacological treatments. However, these methods are unsuccessful in about 40% of women who are then diagnosed as having refractory overactive bladder. For these women, the National Institute for Health and Care Excellence (NICE) recommends urodynamics investigation to identify the diagnosis of detrusor overactivity, before proceeding to invasive treatments including botulinum toxin A (BoNT-A) injection into the bladder wall or sacral neuromodulation.[8]

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Research in context

Evidence before this study

In women with refractory overactive bladder symptoms and urgency predominant mixed urinary incontinence, the UK National Institute for Health and Care Excellence recommends urodynamics investigation to identify the diagnosis of detrusor overactivity before proceeding to invasive treatments such as botulinum toxin A (BoNT-A) injection into the bladder wall or sacral neuromodulation. No previous randomised controlled trial evaluated the clinical-effectiveness and cost-effectiveness of urodynamics in the treatment pathway of women with these conditions.

Added value of this study

The FUTURE study is the largest randomised controlled trial worldwide in this field. The results confirmed that in women with refractory overactive bladder or urgency predominant mixed urinary incontinence, the participant-reported success rates following treatments in women who underwent urodynamics and comprehensive clinical assessment (CCA) are not superior to those who underwent CCA only. Significantly more women who underwent CCA only report earlier improvement in their symptoms. Women in the urodynamics plus CCA group received more tailored treatments but with no evidence of superiority in participant-reported outcomes or fewer adverse events. Urodynamics is not cost-effective at a threshold of £20 000 per quality-adjusted life-year gained in this cohort.

Implications of all the available evidence

The results of the FUTURE Study will lead to changes in the guidelines on the management of urinary incontinence in women and consequently change clinical practice. Women with refractory overactive bladder and urgency predominant mixed urinary incontinence will be offered invasive treatments, such as BoNT-A injection into the bladder wall, based on results from the CCA only. This significant evidence-based change will lead to women experiencing earlier improvement in their quality of life and avoidance of unnecessary invasive investigations. Implementation of our results can lead to significant cost savings to health-care resources in countries with similar health-care systems to the UK.

Urodynamics has been embedded into clinical practice without robust evidence of its clinical-effectiveness or cost-effectiveness.[9] Women's perception of urodynamics vary, with some studies reporting that women find the test embarrassing, invasive, and uncomfortable, but will undergo it if it improves their outcomes.[10–13] Other studies showed urodynamics to be a well accepted and tolerated diagnostic tool.[14–16] However, in women with refractory overactive bladder, urodynamics does not show evidence of detrusor overactivity in up to 45% of cases. Several studies found overactive bladder symptoms improved following treatments irrespective of the presence of detrusor overactivity on urodynamics,[17,18] leading to a debate on the usefulness of urodynamic investigations.

NICE guidelines (CG171)[19] prioritised research to assess the clinical-effectiveness and cost-effectiveness of urodynamics in treatment of refractory overactive bladder in women.

We aimed to compare the clinical-effectiveness and cost-effectiveness of urodynamics plus comprehensive clinical assessment (CCA) versus CCA only in the management of women with refractory overactive bladder symptoms.

Methods

Study design and participants

This was a multicentre, superiority, parallel, open-label, randomised controlled trial (FUTURE) done in 63 secondary (n=35) and tertiary (n=28) hospitals in the UK. The trial protocol was published previously.[20] Participants were women aged 18 years or older with refractory overactive bladder or urgency predominant mixed urinary incontinence of which conservative management (eg, pelvic floor muscle training or bladder retraining, or both, and at least two pharmacological treatments unless contraindicated) was unsuccessful, and were considering invasive treatment. Inclusion and exclusion criteria are listed in the figure. Patients gave written informed consent. FUTURE was approved by the North of Scotland Research Ethics Service (reference number 17/NS/0018). This study is registered with ISRCTN registry (ISRCTN63268739).

Randomisation and masking

Participants were allocated (1:1) to urodynamics plus CCA or CCA only with a remote web-based application, stratified by site and baseline clinical diagnosis (overactive bladder versus urgency predominant mixed urinary incontinence) using random permuted blocks. Clinicians and participants could not be masked to the allocated procedure due to the nature of the interventions.

Procedures

All participants had a non-invasive comprehensive clinical assessment including a detailed medical history, clinical examination, 3-day bladder diary, and bladder scan for post-voiding residual urine volume with or without non-invasive uroflow. Additionally, participants randomly assigned to urodynamics had a urodynamics assessment including cystometry, and uroflow with or without pressure flow studies.

The treatment pathway in the urodynamics plus CCA group was guided by the urodynamics diagnosis in line

with NICE guidelines (CG171).[19,21] The treatment pathway in the CCA-only group was guided by the clinical diagnosis and the non-invasive assessment. The treatment pathways in FUTURE are shown in the appendix (pp 1–2).

A guide for standardising urodynamics practice was developed in conformity with the International Continence Society's good urodynamics practices.[22] A panel of experts prospectively reviewed a random 20% of the urodynamic traces. Feedback, and an action plan when appropriate, were given to the participating sites. Full details of the urodynamic quality assurance process have been described previously.[20]

Participant-reported outcomes were assessed by self-completed questionnaires at baseline and 3, 6, and 15 months after randomisation. An additional questionnaire was completed at 24 months after randomisation by participants whose treatments were delayed due to the COVID-19 pandemic. At 6 and 15 months, participants also completed a 3-day bladder diary and local research nurses did a case-note review.

Outcomes

The primary clinical outcome was participant-reported success at the participants' last follow-up timepoint as measured by the Patient Global Impression of Improvement (PGI-I): success was defined as "very much improved" or "much improved". The primary economic outcome was incremental cost per quality-adjusted life-year (QALY) gained.

Secondary outcome measures were a less strict definition of success defined as "very much improved", "much improved", or "improved"; participant-reported success in the first 2 months following BoNT-A; overactive bladder symptoms measured by the International Consultation on Incontinence Questionnaire (ICIQ) Overactive Bladder (ICIQ-OAB) and the Urgency Perception Scale; urgency and urgency urinary incontinence episodes measured using the 3-day bladder diary; other urinary symptoms measured using the ICIQ Female Lower Urinary Tract Symptoms (ICIQ-FLUTS); health-related quality of life status measured using generic (EQ-5D 5-level [EQ-5D-5L] health status questionnaire) and condition-specific (ICIQ Lower Urinary Tract Symptoms Quality of Life [ICIQ-LUTSQoL]) quality of life questionnaires; adverse events; cost; and cost-effectiveness.

Statistical analysis

FUTURE was powered to detect a minimum of 10% superiority of urodynamics plus CCA over CCA only, where the success rate was assumed to be 60%. For 90% power and a 5% level of significance, 986 participants were required using a χ^2 test with continuity correction,[23,24] inflated to 1096 participants in total (548 participants per group) to allow for 10% attrition in the primary outcome.

The full statistical analysis plan is included in the appendix (pp 3–16). The analysis models included a variable for the baseline diagnosis of overactive bladder compared with urgency predominant mixed urinary incontinence, a variable indicating a participant received a 24-month follow-up, and the time in days from randomisation to follow-up. The latter two variables are included to ensure consistency with the cost-effectiveness modelling. The 24-month account might have generated greater costs and QALYs and delays in data collection might have affected the observed effectiveness of the treatments. Random effects (intercepts) were included for centre and participant (nested within centre) to adjust for multiple observations from the centre and repeated measures over time on the same participants. Dummy variable for time and the interaction of these and the intervention were also included to obtain the treatment effect at the different timepoints. Statistical significance is 5%. The analysis was done with Stata17.

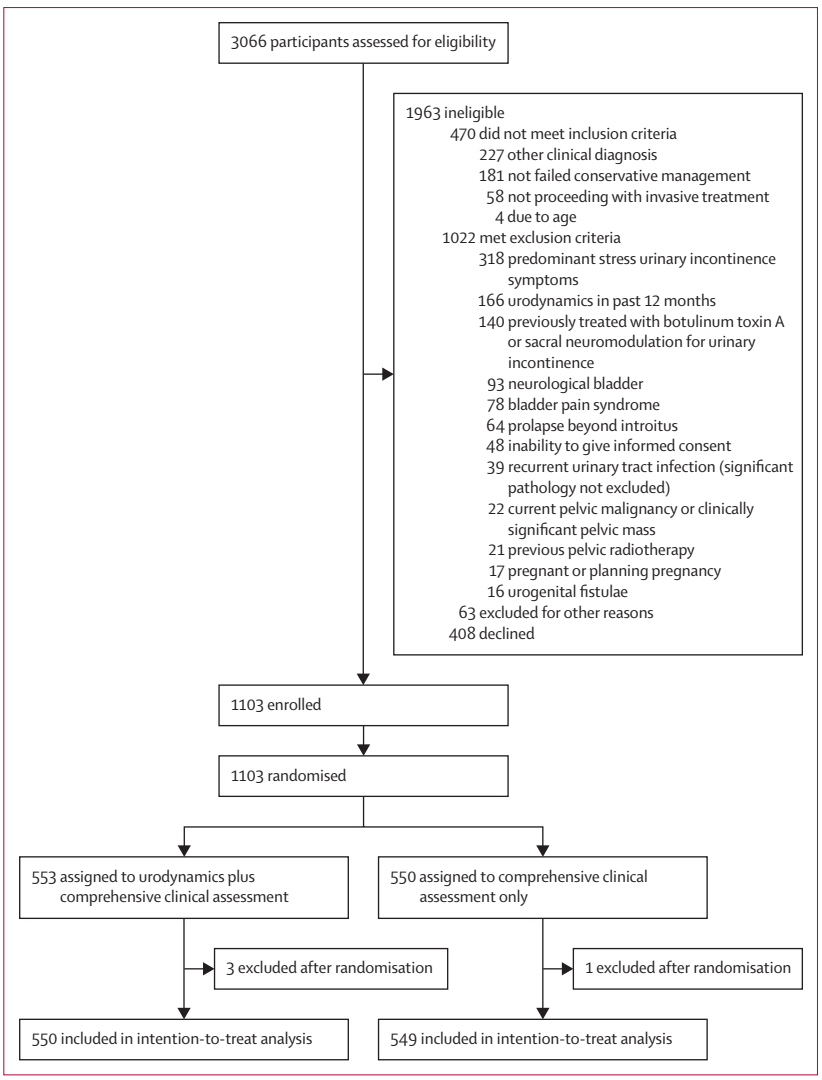

Figure: **Trial profile**

See **Online** for appendix

	Urodynamics plus comprehensive clinical assessment (n=550)	Comprehensive clinical assessment only (n=549)
Age, years	59·3 (14·0), n=550	59·8 (13·1), n=549
BMI, kg/m²	30·6 (6·3), n=540	30·9 (7·1), n=536
>30	263 (47·8%)	257 (46·8%)
>35	120 (21·8%)	141 (25·7%)
Diagnosis		
Overactive bladder	363 (66·0%)	365 (66·5%)
Mixed urinary incontinence	187 (34·0%)	184 (33·5%)
Parity		
0	61 (11·1%)	63 (11·5%)
1	71 (12·9%)	86 (15·7%)
2	235 (42·7%)	204 (37·2%)
≥3	174 (31·6%)	190 (34·6%)
Data missing	9 (1·6%)	6 (1·1%)
Laboratory-confirmed urinary tract infection in the past 12 months		
0	426 (77·5%)	402 (73·2%)
1	64 (11·6%)	69 (12·6%)
2	30 (5·5%)	40 (7·3%)
≥3	30 (5·5%)	36 (6·6%)
Data missing	..	2 (0·4%)
Courses of antibiotics for urinary tract infection in the past 12 months		
0	386 (70·2%)	366 (66·7%)
1	60 (10·9%)	80 (14·6%)
2	45 (8·2%)	47 (8·6%)
≥3	57 (10·4%)	53 (9·7%)
Data missing	2 (0·4%)	3 (0·5%)
Received clean intermittent self-catheterisation training	15 (2·7%)	23 (4·2%)
Previous surgery		
Stress urinary incontinence only	67 (12·2%)	74 (13·5%)
Prolapse only	72 (13·1%)	63 (11·5%)
Prolapse and stress urinary incontinence 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 from previous column)		
Previous conservative treatment		
Bladder training	377 (68·5%)	383 (69·8%)
Pelvic floor muscle training	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%)
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
Urgency Perception Scale		
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%)
Data missing	29 (5·3%)	36 (6·6%)

Data are mean (SD) or n (%). ICIQ-FLUTS=International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms. ICIQ-OAB=International Consultation on Incontinence Questionnaire Overactive Bladder. ICIQ-LUTS=International Consultation on Incontinence Questionnaire Lower Urinary Tract Symptoms. HRQoL=Health Related Quality of Life. EQ-5D-5L=EQ-5D 5-level health status questionnaire. *How much do urinary symptoms interfere is on the scale 0 to 10 with a higher score indicating more interference. †The filling score is on the scale 0 to 16 with a higher score indicating greater symptom severity. ‡The voiding score is on the scale 0 to 12 with a higher score indicating greater symptom severity. §The incontinence score is on the scale 0 to 20 with a higher score indicating greater symptom severity. ¶The ICIQ-OAB score is on the scale 0 to 16 with a higher score indicating greater symptom severity. ‖The ICIQ-LUTSQoL score is on the scale 19 to 76 with higher scores indicating lower HRQoL. **The EQ-5D-5L responses are transformed onto a scale from –0·594 to 1 with higher scores indicating better HRQoL.

Table 1: **Baseline characteristics**

A per-protocol analysis was restricted to women who received their randomised investigation. A subgroup analysis on diagnosis comparing refractory overactive bladder to urgency predominant mixed urinary incontinence was done.

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 as described in the protocol.[20] EQ-5D-5L scores were used to estimate QALYs,[25] whereas costs took the National Health Service perspective and were calculated at 2020–21 price levels using standard sources.[26–28] Increments were estimated using generalised linear regression models with a gamma link. Missing data were imputed at the level of total costs and total QALYs, with the rates for total costs being 23·4% for the CCA-only group and 22·9% for the urodynamics plus CCA group and, for total QALYs, 24·9% for the CCA-only group and 23·9% for the urodynamics plus CCA group. The data were imputed

using multiple imputation by chained equations based on age, prerandomisation diagnosis, length of follow-up, parity, and urgency perception.

Deterministic sensitivity analyses examined a complete case analysis, a societal perspective, an alternative EQ-5D-5L scoring algorithm,[29] and an alternative cost for urodynamic assessment.[30] Probabilistic sensitivity analyses were done. To estimate lifetime effects, a hybrid model with a decision tree describing within-trial events and Markov processes describing long-term events was developed. The model structure was informed by a review of published cost-effectiveness models relating to urodynamic assessment, sacral neuromodulation, BoNT-A, or stress urinary incontinence, which identified four model structures across seven studies.[10,31–36] The most common structure was adopted,[32–35] in preference to the others based on its alignment with the FUTURE trial.

A subgroup of trial clinicians and participants took part in interviews, using a semistructured schedule, to investigate their experiences and preferences for investigation and outcomes. Inductive constant comparison analysis identified emerging themes.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Nov 6, 2017, and March 1, 2021, we screened 3066 participants, of which 1963 were ineligible or declined. We enrolled 1103 participants, and after post-randomisation exclusions (n=4), we randomly assigned 1099 participants to urodynamics plus CCA (n=550) or CCA only (n=549; figure). The baseline characteristics of the two randomised groups were similar (table 1). Two-thirds of participants had a diagnosis of refractory overactive bladder whereas one-third had refractory urgency predominant mixed urinary incontinence at baseline. All participants had unsuccessful conservative management before randomisation (table 1).

Follow-up for the primary outcome was above 90% (table 2). 117 (23·6%) of 496 participants in the urodynamics plus CCA group reported success ("very much improved" or "much improved") on PGI-I compared with 114 (22·7%) of 503 in the CCA-only group (adjusted odds ratio [OR] 1·12 [0·73,1·74]; p=0·60). The per-protocol success rates (113 [24·9%] in the urodynamics plus CCA group and 111 [23·0%] in the CCA-only group; OR 1·22 [95% CI 0·78–1·91]; p=0·39) and the missing data sensitivity analysis (OR 1·04 [0·69–1·57]; p=0·84) were similar (appendix p 17). When the less strict definition of success (ie, including "very much improved", "much improved", or "improved") was used the respective success rates were 217 (43·8%) in the urodynamics plus CCA group and 209 (41·6%) in the CCA-only group (adjusted OR 1·14 [0·79–1·65]; p=0·47). Subgroup analysis did not suggest there was a difference in the effect of urodynamics between participants with overactive bladder and urgency predominant mixed urinary incontinence (appendix p 18). The full PGI-I responses are shown in the appendix (p 19).

In participants who were given BoNT-A, the participant-reported success rates 2 months after injection were 63·8% (88 of 138 participants) in the urodynamics plus CCA group and 60·0% (99 of 165 participants) in the CCA-only group. Using the less strict definition of

	Urodynamics plus comprehensive clinical assessment (n=550)	Comprehensive clinical assessment 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*	507/550 (92·2%)	513/549 (93·4%)	..	..
PGI-I success†				
3 months	34/417 (8·2%)	77/433 (17·8%)	0·28 (0·16–0·51)	<0·0001
6 months	99/475 (20·8%)	122/482 (25·3%)	0·68 (0·43–1·06)	0·090
Last follow-up	117/496 (23·6%)	114/503 (22·7%)	1·12 (0·73–1·74)	0·60
PGI-I success, less strict‡				
3 months	75/417 (18·0%)	114/433 (26·3%)	0·49 (0·31–0·77)	0·0020
6 months	166/475 (34·9%)	203/482 (42·1%)	0·64 (0·44–0·93)	0·020
Last follow-up	217/496 (43·8%)	209/503 (41·6%)	1·14 (0·79–1·65)	0·47
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*	464/550 (84·4%)	493/549 (89·8%)	..	..
PGI-I success, per protocol†				
3 months	30/382 (7·9%)	74/416 (17·8%)	0·26 (0·14–0·49)	<0·0001
6 months	94/437 (21·5%)	120/464 (25·9%)	0·68 (0·43–1·08)	0·10
Last follow-up	113/454 (24·9%)	111/483 (23·0%)	1·22 (0·78–1·91)	0·39
PGI-I success, less strict per protocol‡				
3 months	68/382 (17·8%)	111/416 (26·7%)	0·48 (0·30–0·76)	0·0018
6 months	156/437 (35·7%)	198/464 (42·7%)	0·65 (0·44–0·96)	0·032
Last follow-up	205/454 (45·2%)	204/483 (42·2%)	1·21 (0·83–1·76)	0·32
PGI-I success 2 months after BoNT-A§				
Original definition	88/138 (63·8%)	99/165 (60·0%)	1·17 (0·73–1·89)	0·52
Less strict definition	115/138 (83·3%)	126/165 (76·4%)	1·47 (0·82–2·63)	0·20

Data are n/N (%), unless otherwise stated. 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 overactive bladder. Dummy variables are also included for timepoint and an interaction of these, and the treatment variable is included to allow the treatment effect to be estimated at each timepoint. OR=odds ratio. PGI-I=Patient Global Impression of Improvement. BoNT-A=Botulinum toxin injection 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 but did not respond) then the 15-month questionnaire was their final follow-up. †Success was a participant response of either "very much improved" or "much improved" to the PGI-I question "How would you describe your urinary or bladder problems (urgency or incontinence, or both) now compared to when you joined the study?"; all other responses to the question were considered unsuccessful. ‡A less strict definition in which "improved" was also included in the definition of success. §In the final follow-up, participants who received BoNT-A were asked to describe their symptoms 2 months after their injection on the PGI-I scale.

Table 2: **Participant-reported success rates (PGI-I)**

	Urodynamics plus comprehensive clinical assessment (n=550)	Comprehensive clinical assessment only (n=549)	Mean difference (95% CI)	p value
ICIQ-FLUTS filling 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)	0·37
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 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	–0·28 (–0·60 to 0·03)	0·078
Final follow-up	3·0 (2·7), n=353	2·8 (2·4), n=347	0·24 (–0·08 to 0·57)	0·14
ICIQ-FLUTS incontinence 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	0·66 (0·10 to 1·22)	0·021
Final follow-up	8·1 (5·1), n=350	8·6 (5·1), n=345	–0·19 (–0·77 to 0·38)	0·51
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	0·35 (–0·07 to 0·76)	0·10
6 months	8·2 (3·6), n=381	7·9 (3·7), n=394	0·26 (–0·18 to 0·69)	0·25
Final follow-up	7·6 (3·3), n=352	8·1 (3·5), n=345	–0·43 (–0·88 to 0·02)	0·063
ICIQ-LUTSQoL 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	1·06 (–0·72 to 2·8)	0·24
Final follow-up	44·2 (14·2), n=303	44·9 (15·4), n=292	–0·18 (–2·0 to 1·7)	0·85
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)	0·84
6 months	0·674 (0·300), n=397	0·673 (0·289), n=402	0·011 (–0·016 to 0·038)	0·41
Final follow-up	0·669 (0·295), n=355	0·656 (0·312), n=341	0·015 (–0·013 to 0·043)	0·29
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	0·12 (–0·28 to 0·51)	0·57
Final follow-up	6·0 (3·0), n=355	6·2 (3·0), n=341	–0·13 (–0·54 to 0·28)	0·55

Data are mean (SD), n, unless otherwise stated. ICIQ-FLUTS=International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms. ICIQ-OAB=International Consultation on Incontinence Questionnaire Overactive Bladder. ICIQ-LUTS QoL=International Consultation on Incontinence Questionnaire Lower Urinary Tract Symptoms Quality of Life. EQ-5D-5L=EuroQol Group's 5 dimension health status questionnaire. 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 overactive bladder, 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 timepoint and the interaction of these and the treatment variable are also included in the model to allow the adjusted mean difference at each timepoint to be obtained. *The filling score is on the scale 0 to 16 with a higher score indicating greater symptom severity. †The voiding score is on the scale 0 to 12 with a higher score indicating greater symptom severity. ‡The incontinence score is on the scale 0 to 21 with a higher score indicating greater symptom severity. §The ICIQ-OAB score is on the scale 0 to 16 with a higher score indicating greater symptom severity. ¶The ICIQ-LUTS QoL score is on the scale 19 to 76 with higher scores indicating lower HRQoL. ‖The EQ-5D-5L responses are transformed onto a scale from –0·594 to 1 with higher scores indicating better HRQoL. **How much do urinary symptoms interfere is on the scale 0 to 10 with a higher score indicating more interference.

Table 3: **Secondary outcomes**

success, these were 83·3% (115 of 138) in the urodynamics plus CCA group and 76·4% (126 of 165) in the CCA-only group. These higher success rates support the hypothesis that the waning effect of BoNT-A over time is the main explanation for the lower success rates noted in our subgroup of women receiving BoNT-A in both study groups.

The secondary outcomes are reported in table 3. For urinary symptoms, the ICIQ-FLUTS filling and incontinence scores, and the ICIQ-OAB scores, all show improvement from baseline for both groups with no difference between groups. There were similar patterns for quality of life. At the final follow-up timepoint, ICIQ-OAB scores showed improvement in both groups compared with baseline, with no significant differences between groups. The percentage of women reporting cure or improvement in urgency on the Urgency Perception Scale were similar: 211 (45%) of 469 in the urodynamics plus CCA group versus 194 (42%) of 467 in the CCA-only group. Significantly more participants in the urodynamics plus CCA group reported a higher mean daytime frequency in their 6-month diary (7·1 [SD 2·5], n=162 *vs* 6·6 [SD 2·4], n=180) and adjusted mean difference (0·5 [95% CI 0·1–0·9]; p=0·02). A summary of the results from the follow-up diaries are shown in the appendix (p 20).

Adverse events are shown in table 4. There were 113 (20·6%) of 550 participants in the urodynamics plus CCA group and 122 (22·2%) of 549 in the CCA-only group who had at least one adverse event. The individual event rates were low and there were no obvious differences between groups. The most common adverse events were urinary tract infection and requirement for either prophylactic antibiotics or clean intermittent self-catheterisation. As a greater number of CCA-only participants received BoNT-A, the BoNT-A related adverse events are more common in the CCA-only group.

Treatments received following urodynamics and CCA only are shown in the appendix (p 22). 479 (87·2%) of 549 participants in the CCA-only group received treatments versus 467 (84·9%) of 550 in the urodynamics plus CCA group. There was a greater number of participants receiving BoNT-A in the CCA-only group (343 [71·6%] *vs* 277 [59·3%]). Despite generally low numbers, more participants in the urodynamics plus CCA group received surgery for stress urinary incontinence (16 [3·4%] *vs* 5 [1·0%]), sacral neuro-modulation (11 [2·4%] *vs* 8 [1·7%]), and hydro-distention with or without urethral dilatation (22 [4·7%] *vs* 3 [0·6%]).

Urodynamics diagnosis was available for 494 participants with refractory overactive bladder or urgency predominant mixed urinary incontinence who underwent urodynamics: 287 (58%) were diagnosed with detrusor overactivity or detrusor overactivity incontinence; 65 (13%) had urodynamic stress incontinence; 39 (8%) had urodynamics mixed urinary incontinence; and in 102 (21%) participants, the urodynamics test did not confirm a diagnosis of either urodynamic stress incontinence or detrusor overactivity. The full results of urodynamics and its effect on decision making and treatments received are in the appendix (p 24).[37]

The quality of the urodynamic traces and reports were generally good. Randomly selected urodynamic traces or reports (n=124) were reviewed by a panel of experts. In

only 4% of cases (n=5), our panel disagreed with the diagnosis of the local clinician. These were discussed with the site and the diagnosis changed. Full results of the quality assurance process and results will be published separately.[37]

The within-trial analysis produces marginally higher mean costs (£463 [95% CI 48 to 877]) and QALYs (0·011 [95% CI –0·044 to 0·065]) per patient in the urodynamics plus CCA group (appendix p 28). The higher costs were principally related to the costs of urodynamics and other clinic visits. The incremental cost-effectiveness ratio of £42 643 was associated with a 34% chance of being cost-effective (appendix p 28). When longer-term treatment effects, including treatment discontinuations, were incorporated via modelling, the probability of urodynamics being cost-effective reduced to 23% (appendix p 29). Deterministic sensitivity analysis showed the results were robust to all changes except for the use of complete case results. The full results of the economic analysis will be published separately.[37]

In the qualitative interviews, clinicians described a desire to include urodynamics when they deemed it necessary but would consider its relevance as a routine investigation dependent on the evidence provided through the FUTURE trial. Interviews among FUTURE participants highlighted varying perspectives. Some were prepared to undergo urodynamics to guide improved decision making for their enduring symptoms, whereas others were extremely worried about discomfort and embarrassment, to the point of refusing it. The full results of the qualitative analysis will be published separately.[37]

	Urodynamics plus comprehensive clinical assessment (n=550)	Comprehensive clinical assessment only (n=549)
Urinary tract infection	39 (7·1%)	41 (7·5%)
Using prophylactic antibiotics	40 (7·3%)	36 (6·6%)
Clean intermittent self-catheterisation required	26 (4·7%)	32 (5·8%)
Limb weakness after BoNT-A	8 (1·5%)	16 (2·9%)
Pain during BoNT-A	4 (0·7%)	12 (2·2%)
Urine retention not requiring clean intermittent self-catheterisation	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%)	0
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%)	0
Participant collapsing or feeling faint during urodynamics	2 (0·4%)	0
Burning during urodynamics	1 (0·2%)	0
Numb buttock following sacral neuromodulation	1 (0·2%)	0
Chest infection following surgery	1 (0·2%)	0
Loss of effectiveness following sacral neuromodulation	1 (0·2%)	0
General anaesthetic complication during surgery	1 (0·2%)	0
Dry vagina	1 (0·2%)	0
Urethral bulking pain	1 (0·2%)	0
Groin pain	1 (0·2%)	0
Postoperative pain	1 (0·2%)	0
Nerve pain	0	1 (0·2%)
Tremors	0	1 (0·2%)
Muscle weakness	0	1 (0·2%)
Sickness and nausea	0	1 (0·2%)

Women reported having more than one adverse event. BoNT-A=Botulinum toxin injection A.

Table 4: **Adverse events**

Discussion

The FUTURE study is the largest randomised controlled trial evaluating the clinical-effectiveness and cost-effectiveness of urodynamics investigation in the management pathway of women with refractory idiopathic overactive bladder or urgency predominant mixed urinary incontinence. Our results confirm that the participant-reported success rates following treatments in women who underwent urodynamics plus CCA were not superior to those who underwent CCA only (OR 1·12 [95% CI 0·73–1·74]; p=0·60). We undertook sensitivity analyses and further per-protocol analyses and the effect sizes were consistent with the intention-to-treat estimates, providing confidence in the results. Our results are consistent with Rovner and colleagues[17] and Groenendijk and colleagues[38] who reported that treatment outcomes following BoNT-A and sacral neuromodulation, respectively, were not different in participants with refractory overactive bladder whether they had confirmed detrusor overactivity diagnosis on baseline urodynamics or not.

Our participant-reported success rates at earlier timepoints (3 months and 6 months) showed significant differences between groups favouring CCA only, as women receiving CCA only were more likely to receive their treatment earlier without waiting for the urodynamics test.

Our participant-reported success rates were noted to be lower than those reported in the literature,[18,39] primarily as other studies used a less strict definition of success ("improved" was classed as success) and had significantly shorter follow-up duration. Our secondary analysis with a similarly less strict definition of success showed higher participant-reported success in both groups: urodynamics (43·8%) and CCA-only groups (41·6%). Furthermore, in our subgroup analysis, for women who underwent BoNT-A treatment, the participants' reported success at 2 months after treatment showed similar success rates to those reported in the literature by Brubaker and colleagues[39] and Chapple and colleagues.[18] The effect sizes for both secondary analyses were consistent with

those of our primary analysis providing reassurance in the robustness of results.

Our questionnaire response rates were over 90% at the final timepoint, an excellent achievement in these types of trials, and provide reassurances on the representativeness of the results. We chose the primary outcome (PGI-I) as a global index that is widely used to rate the participants' overall response to treatment received. It is a simple, direct, and easy to use scale that is intuitively understandable to clinicians and patients.[40] We also used two validated disease-specific assessment tools for overactive bladder: the ICIQ-OAB scores and Urgency Perception Scale with no significant differences seen between groups. The results from the PGI-I and the disease-specific tools provide reassurance on the accuracy and reliability of our results.

We further analysed the participant-reported success rates in both groups according to the baseline clinical diagnosis of refractory overactive bladder versus urgency predominant mixed urinary incontinence: the subgroup effects showed no evidence of a significant difference in the effect of urodynamics between groups (1·14 [99% CI 0·33–3·90]; p=0·79). Other studies in the literature did not specifically make a similar comparison.

We assessed the health-related quality of life (HRQoL) in both groups using both general and disease-specific validated tools ensuring robustness of the assessment. The ICIQ-LUTSqol showed improvement in HRQoL compared with baseline in both groups with no difference between groups. However, this was not reflected in the HRQoL scores on the EQ-5D-5L. Similarly, Chapple and colleagues showed more than 5 points improvement in all domains of the Kings Health Questionnaire, except for the general health domain, in participants with refractory overactive bladder who received BoNT-A treatment.[18]

Concerns had been raised previously in the literature about the effect of the quality of urodynamic studies on the reliability of diagnostic results.[41] 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 use and perceived value of that test.[41] Our robust quality assurance system represented a key strength in ensuring the generalisability of our 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 clinical practice in the UK. A key strength is the large number of sites involved in the trial including secondary and tertiary sites ensuring generalisability of our results.

One strength of the FUTURE trial was the embedded qualitative study. Findings regarding embarrassment and distress align with previous studies,[42–44] but experiences vary to include those who have had no discomfort at all. Both clinicians and participants were keen to learn the findings of the FUTURE trial to inform evidence-based decision making and the value urodynamics adds to clinical outcomes given its invasive nature.

In women with refractory overactive bladder or urgency predominant mixed urinary incontinence, urodynamics is shown to be more costly, principally due to the testing itself and more clinic visits. At 2 years, urodynamics is shown not to be cost-effective at a funding threshold of £20 000 per QALY gained, with only a 34% chance of it being cost-effective.

Extrapolation of the estimated 24-month results using final treatment designations and published long-term success rates reduces the probability of urodynamics being cost-effective to 23%. This finding is driven by the higher rates of ongoing treatment with BoNT-A in the CCA-only group, to which the model applies favourable EQ-5D-5L values and long-term success rates.

Finally, we assessed the effect of the urodynamics assessment on the diagnosis and subsequent treatments received in the urodynamics plus CCA group (appendix pp 25–27).[37] Urodynamics clearly changed the diagnosis in 65 (13%) of 487 women with refractory overactive bladder or urgency predominant mixed urinary incontinence to urodynamic stress incontinence, with the potential to change the management plan to urodynamic stress incontinence surgery. Participants in the urodynamics plus CCA group received more tailored treatments according to their urodynamics diagnosis. Less participants in the urodynamics plus CCA group received BoNT-A treatment (277 [59·3%] of 467 *vs* 343 [71·6%] of 479), whereas more received surgery for stress urinary incontinence (16 [3·4%] *vs* 5 [1·0%]), sacral neuromodulation (11 [2·4%] *vs* 8 [1·7%]), and hydrodistention with or without urethral dilatation (22 [4·7%] *vs* 3 [0·6%]). However, these did not lead to superior participant-reported outcomes nor less adverse events in the urodynamics plus CCA group and was not cost-effective.

The majority of participants in FUTURE underwent BoNT-A treatment (appendix p 22), which reflects the practice in the UK but might limit the generalisability of the results to other countries with different practices. This also limited our ability to undertake preplanned secondary analyses of treatment sequences. Women with neurogenic bladder were not included in this study as they have different pathology. Ethnicity was not collected for the trial participants. Follow-up was limited to 15–24 months, hence we lack information on whether women in the CCA-only group would end up having urodynamics at a later stage. Longer-term follow-up at a median of 5 years is under way. Lastly, the effect of the COVID-19 pandemic led to several participants not receiving the intervention or treatments during the original 15-month follow-up period. However, we introduced an additional follow-up timepoint at 24 months for participants who had these delays. The cost-effectiveness analysis is based on NICE guideline thresholds in the UK.

In women with refractory idiopathic overactive bladder or urgency predominant mixed urinary incontinence, the participant-reported success rates following treatment in women who underwent urodynamics and CCA are not superior to those who underwent CCA only. Significantly more women who underwent CCA only report earlier improvement in their symptoms. Urodynamics plus CCA is not cost-effective at a threshold of £20 000 per QALY gained in this cohort.

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MA-F: conceptualisation, funding acquisition, investigation, methodology, supervision, writing—original draft, and writing—reviewing and editing. CC, KG, KW, HH, AsM, KB, and MD: conceptualisation, funding acquisition, investigation, methodology, and writing—reviewing and editing. DC and HB-G: data curation, formal analysis, methodology, visualisation, writing—original draft, and writing—reviewing and editing. SB: funding acquisition, investigation, methodology, project administration, supervision, writing—original draft, and writing—reviewing and editing. PK: formal analysis, investigation, visualisation, and writing—reviewing and editing. SD: conceptualisation, data curation, formal analysis, funding acquisition, methodology, supervision, validation, writing—original draft, and writing—reviewing and editing. NC: conceptualisation, formal analysis, funding acquisition, methodology, supervision, validation, writing—original draft, and writing—reviewing and editing. AG and AlM: conceptualisation, funding acquisition, methodology, validation, writing—original draft, and writing—reviewing and editing. RB, VB, and CK: investigation, project administration, and writing—reviewing and editing. SE and JN: conceptualisation, funding acquisition, methodology, and writing—reviewing and editing. GM: conceptualisation, funding acquisition, methodology, supervision, validation, and writing—reviewing and editing. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. DC and GM have accessed and verified all the data in the study. The views expressed are those of the authors and not necessarily those of the UK National Institute for Health and Care Research (NIHR) or the Department of Health and Social Care.

Declaration of interests

MA-F declares other financial or non-financial interests as a speaker, consultant, or surgical trainer for several industrial companies (Astellas, Ethicon, Bard, Pfizer, AMS, Coloplast, and B Braun) with travel expenses reimbursed, and on occasions received personal honorariums and sponsorship towards attending scientific conferences; a research grant from Coloplast managed by University of Aberdeen; a small number of supported trainees who attended pharmaceutical sponsored educational or leadership workshops or received assistance towards presenting their research work at scientific conferences; being a previous chair of the Scottish Pelvic Floor Network, which at the time received sponsorship by various industrial companies and fees to exhibit in annual meetings and surgical workshops; receiving travel sponsorship and occasional speaker fees from numerous national and international conferences and non-profit organisations when invited as guest speaker or expert surgeon; and in 2019, at request from NHS Grampian, attended two educational meetings for setting up sacral nerve stimulation service partially funded by Medtronic. CC declares receiving consulting fees from Coloplast, Ingenion, MUVON Therapeutics, Pierre Fabre, ProVerum, Takeda, and Urovant; support for attending meetings or travel from the European Association of Urology and King Faisal Specialist Hospital and Research Centre; patents planned, issued, or pending with the University of Sheffield; participation on a data safety monitoring board or advisory board for Coloplast, Ingenion, Pierre Fabre, and ProVerum; leadership or fiduciary role in other board, society, committee, or advocacy group as Past Secretary General of the European Association of Urology until March, 2023; and other financial or non-financial interest with Astellas as an author (non-financial). DC reports grants or contracts from the NIHR Health Technology Assessment funding for long-term follow-up of the MASTER and SIMS trials. HB-G declares grants or contracts from Merck Sharp & Dohme; and royalties or licences from the National Institute for Health and Care Excellence. KG declares payments for expert testimony as a Medicolegal advisor. NC declares participation on a data safety monitoring board or advisory board for the International Consultation on Incontinence Questionnaire Advisory Board; leadership or fiduciary role in other board, society, committee, or advocacy group for the Association for Continence Advice Executive Committee (unpaid) and Royal College of Nursing Bladder and Bowel Forum Steering Committee (unpaid). KW declares leadership or fiduciary role in other board, society, committee, or advocacy group as Chair of British Society of Urogynaecology (2021–23; unpaid), Vice Chair of British Society of Urogynaecology (2019–21; unpaid), and Topic Lead Urinary Incontinence – National Institute for Health and Care Excellence Guideline NG123: urinary incontinence and pelvic organ prolapse in women: management (2017–20; honorarium for attending meetings and travel). HH declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events for Medtronic, Laborie, and Allergan; leadership or fiduciary role in other board, society, committee, or advocacy group for European Association of Urology male lower urinary tract symptoms guidelines, Associate Editor *British Journal of Urology International*, and Associate Editor *Neurourology & Urodynamics*. AM declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events for Contura; payment for expert testimony for Kennedys Law; support for attending meetings and travel from Contura; leadership or fiduciary role in other board, society, committee, or advocacy group as chairman of industry liaison committee European Urogynaecological Association; and stock or stock options with Atlantic Medical and Viveca Biomed. MD declares grants or contracts from the Rosetrees Trust (chief investigator), NIHR Health Technology Assessment (project NIHR131984 and NIHR 131172, co-investigator) Medical Research Council (project MR/V033581/1, co-investigator), and Engineering and Physical Sciences Research Council (project

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Data sharing

Individual participant data collected for this trial and a data dictionary defining each field in the dataset will be made available to others; all available participant data will be de-identified. The protocol, statistical analysis plan, informed consent form, and ethics committee approval are available. To access data, a request should be submitted to the corresponding author with a scientific proposal including objectives. Written proposals will be assessed by members of the FUTURE trial steering committee and a decision made about the appropriateness of the request. Data will only be shared after a data sharing agreement is fully executed.

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