Female Urgency, Trial of Urodynamics as Routine Evaluation

FUTURE Study - Female Urgency, Trial of Urodynamics as Routine Evaluation; a superiority randomised clinical trial to evaluate the effectiveness and cost effectiveness of invasive urodynamic investigations in management of women with refractory overactive bladder symptoms.

PROTOCOL

A UK Collaborative Trial funded by the National Institute of Health Research (NIHR), Health Technology Assessment (HTA) Programme (project number 15/150/05)

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Signatures
By signing this document I am confirming that I have read, understood and approve the protocol for the above study.

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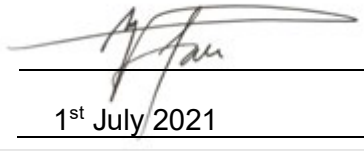
Signature: 

Date: 1st July 2021

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VERSION HISTORY:

Amendment no.	Protocol version no.	Description of changes (*incl. author(s) of changes*)	Date of Protocol
	Version 1	New Document	
1	Version 2	Changes made following HTA review. Randomisation section has also been amended.	01/09/2017
2	Version 3	Changes made following review by the TSC. Clarification of exclusion criteria and health economic analyses	01/02/2018
3	Version 4	Inclusion of participant identification centres	01/10/2018
4	Version 5	Clarification on outcomes collected at 3 months and extension to the recruitment phase/end of study	01/05/2019
5	Version 6	Amendment to the contact/consent process in the qualitative study (contact by email and verbal consent added)	01/10/2019
6	Version 7	Amendment to recruitment end date following COVID-19 suspension	01/07/2020
7	Version 8	Inclusion of a secondary outcome measure as suggested by DMC; correction of response categories for PGI-I; update to tariffs used to estimate QALYs; textural changes ahead of publication	01/11/2020
8	Version 9	Appendix added detailing implications of COVID-19 (recruitment and follow-up)	01/12/2020
9	Version 10	Correction to the assessment period for AEs and SAEs	01/07/2021

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PROTOCOL SUMMARY

Question addressed:	In women with refractory OAB, is urodynamics and comprehensive clinical assessment associated with superior patient reported outcomes following treatment and is more cost-effective, compared to comprehensive clinical assessment only.
Considered for entry	We are recruiting 1096 women aged ≥18 years, with refractory OAB symptoms, across approximately 60 secondary and tertiary care hospitals in the UK Eligible women are women aged ≥18 years with refractory OAB or urgency predominant MUI who are considering invasive treatment after failed both conservative treatment and pharmacological treatment.
Inclusion/Exclusion Criteria	Exclusion criteria are: Predominant SUI symptoms; Previous urodynamics in the last 12 month; 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/ SNM for UI; Previous pelvic radiotherapy; Prolapse beyond introitus; Pregnant or planning pregnancy; Recurrent UTI where a significant pathology has not been excluded; Inability to give an informed consent.
Interventions	**1. Urodynamics plus comprehensive clinical assessment** **2. Comprehensive clinical assessment only**
Outcomes	The primary outcome measure is participant reported success at 15 months post-randomisation (approximately 12 months post-treatment) as measured by the Patient Global Impression of Improvement - Index (PGI-I). The primary economic outcome is the incremental cost per quality adjusted life year (QALY) gained of urodynamics and comprehensive clinical assessment compared to comprehensive clinical assessment only, modelled over the lifetime of the patients.
Co-ordination	**Local**: by local research teams **Central**: by Trial Office in Aberdeen (Telephone 01224 438405). **Overall**: by the Project Management Group and overseen by the Trial Steering Committee and the Data Monitoring Committee.

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
B&BF	Bowel and Bladder Foundation
BoNT-A	Botulinum Toxin injection
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CISC	clean intermittent self-catheterisation
COB	Cystitis and Overactive Bladder
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
DO	Detrusor Overactivity
DOI	Detrusor Overactivity Incontinence
EQ-5D-5L	EuroQol Group's 5 dimension health status questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ICIQ-FLUTS	International Consultation on Incontinence Questionnaire - Female Lower Urinary Tract Symptoms
ICIQ-LUTSqol	International Consultation on Incontinence Questionnaire – Lower urinary tract symptoms Quality of Life
ICIQ-OAB	International Consultation on Incontinence Questionnaire – Overactive Bladder
ICMJE	International Committee of Medical Journal Editors
ICS	International continence Society
ISD	Information Statistics Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Information Technology
ITT	Intention-To-Treat
IVR	Interactive Voice Response (randomisation)
MDT	Multidisciplinary team
MRC	Medical Research Council
MUI	Mixed Urinary Incontinence
NCT	National Clinical Trial
NHS	National Health Service
NHSG	National Health Service Grampian
NICE	National Institute for Health and Care Excellence
NIHR	National Institute Health Research
NRES	National Research Ethics Service

OAB	Overactive bladder
PFMT	Pelvic Floor Muscle Training
PGI-I	Patient Global Impression of Improvement
PI	Principal Investigator
PIC	Participant Identification Centre
PIL	Patient Information Leaflet
PMG	Project Management Group
PP	Per Protocol
PPI	Patient and Public Involvement
PQ	Participant Questionnaire
QALY	Quality Adjusted Life Year
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research nurse
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SNM	Sacral Neuro-Modulation
SOP	Standard Operating Procedure
SOPs	Standard Operating Procedures
TMF	Trial Master File
TSC	Trial Steering Committee
UDS	Urodynamics study
UI	Urinary Incontinence
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen
UPS	Urgency Perception Scale
USI	Urodynamic Stress Incontinence
UTI	Urinary Tract Infection
UUI	Urgency Urinary Incontinence

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2 CHaRT Director
3 Trial Managers
4 Data Co-ordinator
7 Senior Trial Manager
8 Senior IT Manager
9 Trial statistician

Project Management Group (PMG)

This group comprises of the grant holders along with representatives from the Trial Office Team and will be co-chaired by the CI and Prof Chris Chapple or delegate.

Trial Steering Committee (TSC) Members

The membership of this committee comprises independent members along with the Chief Investigator or a nominated delegate. Other FUTURE grant-holders and key members of the Trial Office Team (e.g. the trial manager) may attend TSC meetings. The TSC Charter details the membership with names and contact details and terms of reference of the TSC. This is filed in the Trial Master File (TMF).

Data Monitoring Committee (DMC) Members

This committee is comprised of independent members, and the trial statistician contributes as appropriate. The CI and/or a delegate may contribute to the open session of the meetings as appropriate. The DMC Charter details the terms of reference of the DMC and the names and contact details. This is filed in the Trial Master File.

1. INTRODUCTION

1.1 Background

Overactive bladder (OAB) syndrome has been defined by the International Continence Society (ICS) as urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, in the absence of any other pathology .[1]

The Leicestershire MRC (Medical Research Council) Incontinence Study showed a 21% overall prevalence of OAB in women aged ≥40 years in the United Kingdom (UK); UUI and mixed urinary incontinence (MUI) represented 11% and 36% of these women respectively.[2] The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) study reported relatively higher UUI prevalence rates of 13.3% for men and 30.3% for women in the United States.[3] In 2016, Komeso reported a large epidemiological study showing that the prevalence of urinary incontinence (UI) increases with age; this was most apparent for UUI and MUI: the odds of occurrence of UUI were 2 and 9 fold increased in the 7th and 10th decades, compared with the 6th decade (OR 2.18; 95%CI=1.5–3.15 and OR=9.19; 95%CI=5.56–15.20) respectively.[4] The prevalence of MUI also significantly increased in the 8th to10th decades (both P≤0.005) but interestingly, the prevalence of Stress Urinary Incontinence (SUI) did not seem to increase with age in this study. Similar results were shown by the EPINCONT study of 28,000 women.[5] The EPIC prevalence data estimates that the worldwide number of adults aged ≥20 year with UUI or MUI was 103 million in 2008, with projected increase to 127 million in 2018.[6] Therefore the prevalence of OAB/MUI is likely to increase in the years to come, especially given the ageing population in the UK.

OAB and UUI have been shown to have a negative impact on a woman's social, physical and psychological wellbeing; leading to embarrassment, low self-esteem, and negative effects on the productivity of working women. In extreme cases, women reported avoiding employment because of fear of embarrassing situations;[2,7] 60% avoided going away from home; and 50% reported avoidance of sexual activity.[8] This debilitating social problem has significant cost implications to the health resources in the UK. The total annual cost to the NHS is £301 million or 0.3% of the total NHS budget in 2009.[9] Costs borne by women and their families (e.g. for containment products, etc.) were £230 million.[10] Health related costs for management of OAB and UUI was estimated at approximately €7.0 billion in 2005 across 6 countries: Canada, Germany, Italy, Spain, Sweden, and the UK.[6]

The National Institute for Health and Care Excellence (NICE) shows the standard benchmark rate for a referral into a UI service for UK women is 0.8% (800 per 100,000 adult female/ year).[11] In women diagnosed with OAB, the NICE Guideline CG171 recommends initial conservative treatment which includes: lifestyle modifications, bladder training and pelvic floor exercise and pharmacological therapy (anticholinergics and/or beta-3 agonist). However, these measures are unsuccessful for approximately 25 - 40% of women (i.e. refractory OAB).[12] For these women, NICE recommends "urodynamics" investigation to confirm the diagnosis of detrusor overactivity (DO) before proceeding to invasive treatments such as Botulinum Toxin-A injection (BoNT-A) or sacral neuro-modulation (SNM).[11] NICE CG171 was the relevant guideline at time of the FUTURE study planning, however the recommendation has not changed in the updated NICE NG123.[13]

Invasive urodynamics is a diagnostic test that involves the insertion of 1 to 2 catheters into the bladder and another one into the vagina or the rectum. The rationale for urodynamics is to reproduce the women's symptoms and to identify the underlying pathology. During bladder filling, (DO) may be seen; 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 MUI. Urodynamics can also identify other pathology for example bladder outlet obstruction or detrusor underactivity; which may influence the choice of therapy.

Although urodynamics is currently the recommended investigation in the NICE guidelines for the assessment of women with refractory OAB and /or MUI,[11,13] the clinical and cost effectiveness of urodynamics have not been demonstrated in well designed, adequately powered clinical trials. Interestingly, the current evidence on the value of urodynamics in these women suggests little impact, if any, on the post-treatment patient reported outcomes.[14]

Invasive treatments for refractory OAB: Current guidelines recommend BoNT-A or SNM as the treatments for women with refractory OAB following failure of conservative and medical treatment.[11,13]

A) BoNT-A treatment is an injection into the bladder wall using a cystoscope (rigid or flexible), either under general or more commonly local anaesthesia. The treatment, if successful, is usually repeated every 6 to 12 months.

In women with refractory OAB and associated DO on urodynamics: Brubaker *et al*. showed that approximately 60% who received BoNT-A had a positive clinical response on the Patient Global Impression of Improvement scale (PGI-I).[15] Secondary analyses from two recent RCTs of BoNT-A versus placebo, suggested that successful treatment outcomes did not appear to be related to the pre-operative urodynamics diagnosis of DO.[14,16] Chapple et al (2013), in a double blind, placebo controlled RCT showed that BoNT-A significantly improves all symptoms of refractory OAB and quality of Life (QoL); there was no impact of the pre-operative diagnosis of DO on the treatment outcomes.[16] Similarly, Rovner *et al*. (2011) in a placebo controlled RCT showed 57% of the patients were satisfied compared to 19% placebo at 3 months following BoNT-A treatment, irrespective of the presence of DO on urodynamics.[14] BoNT-A is now licenced in the UK for treatment of idiopathic refractory OAB symptoms (with symptoms of urinary incontinence, urgency and frequency) without the need for pre-operative urodynamics.[17]

In a recent observational study embedded within the BUS RCT 666 women with non-refractory OAB underwent urodynamics; the results suggested that clinicians and patients appeared to be guided in part by the urodynamics diagnosis in selecting treatment options.[18] 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.[18] 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.

B) **Sacral Neuromodulation (SNM):** The principle of SNM is that electrical stimulation of the sacral reflex pathway will inhibit the reflex behaviour of the bladder. SNM is a two-stage procedure; stage one is a SNM test 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 (permanent 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 the unique advantage that patient outcomes are assessed before a commitment is made to the permanent procedure.

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 (n=58); at 3 years, 46% were dry and 13% improved.[19-21] In one RCT, patients with urgency and frequency showed improvements in several SF-36 domains in the active treatment group (n=51; 90% women) at 6

months follow-up.[21] 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.[11] Around one third of patients may require reoperation, most often due to pain at the implant site, infection, or the need for adjustment and modification of the lead system. Interestingly, while urodynamics investigation is considered a standard practice prior to SNM treatment in NICE CG171 and NG123, confirmation of DO is not.[11,13] One recent observational study reported that pre-operative diagnosis of DO was not a prerequisite selection criterion for SNM.[22]

Sequence of Treatment in women with refractory OAB: The best sequence of interventions for women with refractory OAB is not known**.**

In 2013, NICE CG171 included a heath economic evaluation which suggested that BoNT-A was a cost-effective intervention in comparison with either no active treatment or SNM and NICE recommended offering BoNT-A as first intervention to women with refractory OAB and DO.[11] They recommended SNM for women unable to catheterise or who have a cultural or ethical objection to catheterization (slightly amended in NG123 to women unprepared to accept risks of clean intermittent self-catheterisation (CISC) with BoNT-A), or those with persistent symptoms following BoNT-A treatment.[11,13]

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.[23] Most recently, Marcelissen *et al*. showed that only 30% of their patients initiated on BoNT-A treatment were still on treatment at minimum follow-up of 5 years; the majority of patients who discontinued treatment (98%) did so after the 1st or 2nd injection.[24] In an economic model comparing SNM with BoNT-A over a five year period with a societal perspective, *Leong et al*. reported a greater gain in quality adjusted life years (QALY) and a greater associated cost savings when patients were initiated on SNM treatment.[25] As the QALY gain from BoNT-A injection was lower due to the loss of effect with re injections over time, SNM became cost-effective after five years compared with BoNT-A, with an incremental cost-effectiveness ratio of 27,991 Euros, within the accepted NICE threshold of £20,000 to £30,000.

Accordingly, UK practice varies and usually relies on treatment options available locally within the units. Our brief survey of the potential collaborating centres for the FUTURE study suggests a considerable number of units and surgeons offer BoNT-A treatment for women with refractory OAB with and without urodynamics evidence of DO. In addition, in tertiary units where SNM may be readily available, surgeons tend to offer women with confirmed DO the choice between BoNT-A or SNM 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 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”.[11]

1.2 Rationale for the trial

Research Question:

Does routine urodynamics investigation in addition to comprehensive clinical assessment improve patient-reported outcomes following treatment, compared to comprehensive clinical assessment only, in women with refractory OAB symptoms and is it cost-effective?

Rationale: NICE recommends urodynamics investigation to confirm the diagnosis of DO in women with refractory OAB before proceeding to invasive treatment.[11]

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%.[26] The accuracy of urodynamics relies on well calibrated equipment, experience of investigators and their objective interpretation of a number of subjective parameters. Standardisation of urodynamics is difficult and is influenced by wide variation in staff practice and equipment used.[27] These factors raise a valid debate on the clinical and cost-effectiveness of urodynamics and whether it actually improves the outcomes of subsequent treatments compared to treatment guided by comprehensive clinical assessment only.

From the patients' perspective, many describe urodynamics as an invasive and embarrassing investigation and associated with an element of emotional distress.[28,29] Urodynamics is also associated with a risk of discomfort and urinary tract infection.[18] However the majority of women find it acceptable if it will improve their outcomes post-treatment.[18,30-32] 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 development of the study protocol). 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 one such test that has been embedded in clinical practice without robust evidence of its clinical or cost-effectiveness. Current evidence shows urodynamics to have no impact on the patient reported outcomes following conservative treatment of UI[33] and for those undergoing surgical treatment for symptoms of pure SUI.[34] Accordingly, NICE CG171 has prioritised research to assess the clinical and cost-effectiveness of urodynamics in treatment of refractory OAB.[11]

The outcome of the FUTURE study would inform patients, clinicians and policy makers whether routine urodynamics investigation improves the treatment outcomes in women with refractory OAB and whether it is cost-effective.

2. TRIAL AIM AND OBJECTIVES

Hypothesis: In women with refractory OAB, urodynamics and comprehensive clinical assessment is associated with superior patient reported outcomes following treatment and is more cost-effective, compared to comprehensive clinical assessment only.

The **primary objectives** are to:

1. Evaluate whether routine urodynamics investigation and comprehensive clinical assessment significantly improves patient reported success rates following treatment, compared to comprehensive clinical assessment only;
2. Assess the cost-effectiveness of routine urodynamics investigation and comprehensive clinical assessment, compared to comprehensive clinical assessment only.

Secondary objectives are to:

1. Assess the above outcomes in pre-specified subgroups of women: OAB and urgency predominant MUI.
2. Explore the clinicians' attitudes towards urodynamics investigation and its influence on surgical decision making;
3. Explore the participants attitudes and experience in both pathways;

4. Explore the clinical and cost-effectiveness of the different sequence of treatments for refractory OAB

3. TRIAL DESIGN

A pragmatic multicentre superiority randomised controlled trial comparing the effectiveness and cost-effectiveness of routine urodynamics investigation and comprehensive clinical assessment versus comprehensive clinical assessment only in the management of women with refractory OAB symptoms (Figure 1). An internal pilot study with stop/go criteria is embedded within the RCT to establish whether the projected recruitment rate is achievable.

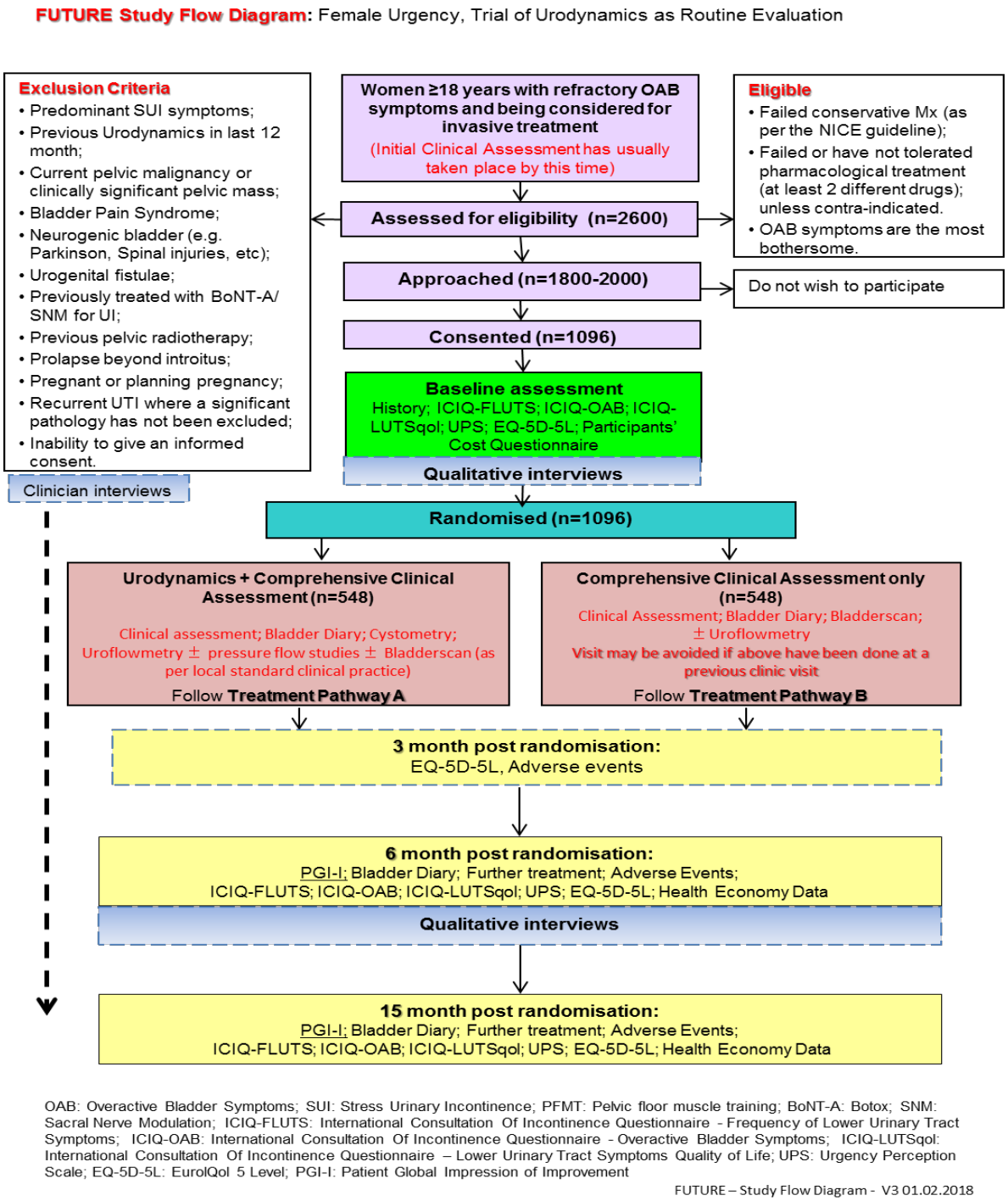

Figure 1: Study Flow Diagram (Also see appendix 1)

Rationale for Superiority design: Urodynamics has become standard clinical care without a solid evidence to support its routine or selective use, as highlighted by the NICE guideline CG171;[11] therefore a superiority type design was adopted to provide the first randomised trial evidence to confirm or refute the clinical and cost-effectiveness of urodynamics over comprehensive clinical assessment only. We surveyed the opinion of the potential collaborating units including Urologists and Urogynaecologists, practicing in district general, teaching and tertiary units in the UK. The responses showed an overwhelming support for a superiority design however there was a wide variation in the minimum superiority margin accepted by clinicians (range 10%-50%). The consensus was that, given that urodynamics is costly in both time and resources, and can be embarrassing for the women, a minimum superiority margin of 10% improved patient reported outcomes would be required for the NHS to adopt routine urodynamics investigation over and above comprehensive clinical assessment in women with refractory OAB.

3.1 Intervention being evaluated

The RCT compares: "urodynamics and comprehensive clinical assessment" versus "comprehensive clinical assessment only".

3.1.1. Comprehensive clinical assessment includes:

- Detailed history including:
    - 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
    - Past medical or surgical history of relevance

- Clinical examination including assessment for:
    - Stress urinary incontinence
    - Pelvic organ prolapse
    - Pelvic masses and other pelvic pathology

- Non invasive clinical assessments are also performed:
    - Evaluation of Bladder Diary for 3 days to assess daytime frequency; nocturia; urgency and UUI episodes (N.B. A minimum of 24 hours completed diary will be accepted as a valid diary. Diary completed at a previous clinic visit within last 3 month will be accepted)
    - Post voiding residual urine volume using ultrasound bladder scanning (some units may perform non-invasive free uroflowmetry).

3.1.2. Urodynamics refers to the comprehensive invasive and non-invasive assessment of women with urinary symptoms and include: detailed history, examination and bladder diary as above; Cystometry; free uroflowmetry ± pressure flow studies ± bladder scan.

Standardisation of urodynamics practice

To be assured of good quality measurements and accurate urodynamics data recording, a "FUTURE study Guide for Urodynamics Best Practice" has been developed in conformity with the 2016 ICS Good Urodynamics Practices.[35]

Clear guidance for urodynamic trace marking have been developed to standardise the points used for data in each study, and make central reading/ audit of traces more reliable.

Prior to performing the first randomised urodynamics test within the FUTURE Study, collaborating units are required to

- Undertake urodynamics machine calibration checks for measurements, and

- Submit two anonymous urodynamics traces with their reports for central reading and review by a panel of experts within the FUTURE study team. Feedback is given to centres for any improvement steps needed.

During the course of the study:

- Collaborating units will submit copies of urodynamics traces/reports for all participants that are randomised to the urodynamics arm for archiving as study data.
- Random central check of traces/reports will be undertaken after ten traces/reports are submitted per unit (five for low recruiting units) by the panel above for quality assurance. If required, one to one feedback will be provided and closer monitoring (random central checks after five traces/reports) undertaken.

Web-based training on best urodynamics practice is available for collaborating units. An expert clinical engineer (co-investigator) provides one to one support for collaborating units if/when required.

Full details are in the "FUTURE study Guide for Urodynamics Best Practice".

Defined Treatment Pathways

In the current clinical practice, NICE recommends urodynamics investigation in women with refractory OAB, to confirm the diagnosis of DO, prior to offering invasive treatment (such as BoNT-A or SNM) and within the context of MDT approach.

In the urodynamics plus comprehensive clinical assessment arm of the study (Pathway A – Appendix 1): The treatment pathway is guided by the urodynamics diagnosis and is in line with the NICE guideline (CG171).[11] The latter recommends BoNT-A 200 units as the first treatment, however since its publication, further evidence confirmed the efficacy of BoNT-A treatment at the lower dose of 100 units with less adverse events[36] and it has since been licensed in that dose.[13]

NICE CG171 also recommends offering SNM treatment for patients who are unable or un willing to perform CISC or following un successful BoNT-A treatment pending MDT discussion.[11] However, in view of the lack of robust evidence on the best sequence of treatments in women with refractory OAB, participants in both arms of the FUTURE study can be offered either BoNT-A (100 units) or the SNM test; the decision will be discussed in the local MDT or as per local standard best practice. This approach will vary between units depending on their local clinical practice and the availability of treatments. Participants with other diagnoses on urodynamics would be offered the appropriate treatments.

Depending on the clinical outcome of treatment; participants with persistent or de-novo symptoms are offered urodynamics tests and treatment accordingly or further/ repeat treatment according to comprehensive clinical assessment only.

In the comprehensive clinical assessment only arm of the study (Pathway B - Appendix 1): The treatment pathway is guided by the clinical diagnosis and non invasive tests. Considering the evidence above, participants with clinically diagnosed refractory OAB or urgency predominant MUI are offered either BoNT-A (100 units) or SNM test. The decision will be discussed in the local MDT or as per local standard best practice. This approach will vary between units depending on their local clinical practice and the availability of treatments. Participants with other clinical diagnoses (such as overflow incontinence or SUI predominant MUI) are offered other appropriate treatments such as CISC, SUI surgery or other medical/ conservative treatments as per local standard best practice.

Depending on the clinical outcome of initial treatment: participants with persistent or de-novo symptoms will be offered urodynamics and treatment accordingly or may consider repeat/

further treatment according to comprehensive clinical assessment only (e.g. patients with persistent OAB symptoms following treatment with 100 units of BoNT-A treatment may be offered the option of repeat BoNT-A treatment).

Deviation from the treatment pathways may occur depending on the local clinical practice and the availability of treatments in the participating units. However, patterns of deviations will be assessed by the CI (or delegate).

4. TRIAL RECRUITMENT

4.1 Trial population

We are recruiting 1096 women aged ≥18 years, with refractory OAB symptoms, across approximately 60 secondary and tertiary care hospitals in the UK

4.2 Inclusion and exclusion criteria

Eligible women are women aged ≥18 years with refractory OAB or urgency predominant MUI (I.e. in whom OAB are their most bothersome symptoms), and

- have failed conservative management (as per NICE guideline e.g. pelvic floor muscle training/ bladder retraining) ***and***
- have failed or have not tolerated pharmacological treatment (at least 2 different drugs) unless contra indicated ***and***
- are being considered for invasive treatment.

Exclusion criteria are:

- Predominant SUI symptoms;
- Previous urodynamics in the last 12 month;
- 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/ SNM for UI;
- Previous pelvic radiotherapy;
- Prolapse beyond introitus;
- Pregnant or planning pregnancy;
- Recurrent UTI where a significant pathology has not been excluded;
- Inability to give an informed consent.

4.3 Identifying and approaching participants

All potentially eligible women are identified by their local research team at outpatient clinics or waiting lists for urodynamics/outpatient clinics in each recruiting centre. Participant identification centres (PICs) may also identify potential patients. Posters within appropriate clinics provide information about the study. Local procedures at the participating hospitals will vary and the timing and mode of approach to women and the consent process may accommodate both the specific circumstances at each site and the needs of the women.

Each eligible woman will be given or sent a patient information leaflet (PIL) describing the FUTURE study and will have the opportunity to discuss the study with her consultant. Women may also receive their local hospital PIL regarding the urodynamics investigation. Women will have the opportunity to discuss all aspects of the proposed research with the local clinical team (consultant/ staff at clinics), the research nurse (RN), and if appropriate, general practitioner (GP), family and friends.

Women may make a decision to participate during an initial consultation with their consultant or during a subsequent visit to hospital (e.g. a clinic appointment) or alternatively at home.

Eligible women may receive a telephone call from the local RN to discuss any queries and arrange a baseline assessment visit. Women who decide to participate can be sent or given the study documents (consent form and baseline questionnaires) to complete at home. They can either send their completed documents (consent form and baseline questionnaire) through the post to the local team at their treating hospital or bring it with them if they are returning to hospital for another consultation or assessment.

The PIL refers to further embedded research within the FUTURE study and participants indicate on the study consent form, if they accept /or not to be contacted by the qualitative research team for the qualitative study as detailed below in section 11. In addition, the PIL and consent form refer to the possibility of, and seek the participants' consent to, be contacted for longer term follow up of the FUTURE study to further assess the clinical and cost-effectiveness outcomes (section 6.6).

A log will be kept of all potentially eligible patients assessed in order to document the reasons for non-inclusion in the study (e.g. reason they were ineligible or declined to participate) to inform the CONSORT diagram. Brief details of potentially eligible patients will be recorded in the screening logs at each site (these are an aid to monitoring potential participant inclusion). All women who enter the study will be assigned a unique Study Number.

4.4 Informed consent

Women are given ample time to read and understand the fully comprehensive FUTURE study PIL and are given opportunities to obtain answers for any queries they may have before taking their informed decision on whether to join the study and signing the study consent form. Women who cannot give informed consent (e.g. due to incapacity) are not eligible for participation.

Signed consent forms are obtained from the study participants in all centres by GCP trained members of the local research team (see 12.2). The participant's permission is sought to inform their GP that they are taking part in this trial.

Consent forms that are returned by post are checked, signed and dated with the date of receipt. No study specific activities take place before consent is given.

4.5 Randomisation and allocation

After completing the baseline assessment, eligible and consenting participants, , will be randomised to either "urodynamics and comprehensive clinical assessment" or "comprehensive clinical assessment only" using the randomisation application at the trial office at the Centre for Healthcare Randomised Trials(CHaRT), University of Aberdeen. Full descriptions of the interventions are detailed in section 3.1.

This randomisation application will be available 24 hours a day, 7 days a week as a web-based application. The randomisation uses stratified random permuted blocks with (a) centre; and (b) diagnosis of OAB versus Mixed Urinary Incontinence used as stratum. In addition, a random component is used in the minimisation algorithm to ensure concealment of the allocation.

The Principal Investigator (PI) at site, or member of the local research team (with delegated authority), accesses the web based or telephone system. Stratification characteristics are entered into the voice-activated or web-based system, which returns the allocation status. Participants are informed of their allocated pathway following randomisation. If the participants are not present at the time of randomisation, they are contacted by the research team to inform them of the allocated pathway after randomisation. Participants who have consented to take part in the embedded qualitative study are informed with their allocated pathway after their initial qualitative interview.

In both study arms, participants are offered evidence-based treatments for refractory OAB according to their diagnosis and as per the defined treatment pathways (Appendix 1) which were developed in line with the NICE guideline CG171.[11]

4.6 Administration arrangements post recruitment

Following trial entry:
The Study Office in Aberdeen:

i) Informs the participant's GP (by letter enclosing information about FUTURE and Study Office contact details) if the participant consents for this.
ii) Inform the qualitative study team of those participants' consenting for a contact by them.

The local Research Nurse/Recruitment Officer and/or PI will:

- file a copy of the consent form in the local hospital records along with information about the study, give one copy to the patient; file one copy to the local site file and send one copy, by post (Royal Mail), to the Study Office in Aberdeen;
- enter study data regarding the participant into the bespoke study website;
- maintain study documentation at site;
- provide any relevant follow-up clinical data.

GPs are asked to contact the Study Office if participants moves, becomes too ill to continue or dies, or any other notifiable event or possible serious adverse event occurs. Alternatively, staff at the Study Office may contact the GP if, for instance, a postal questionnaire is returned to the Study Office with incorrect address.

5. OUTCOME MEASURES

5.1 Primary outcome measure

The primary outcome measure is participant reported success at 15 months post-randomisation (approximately 12 months post-treatment) as measured by the Patient Global Impression of Improvement - Index (PGI-I).

The PGI-I is a validated single item questionnaire designed to assess the participant's impression of changes in her urinary symptoms. The PGI-I asks the participant to best describe her urinary symptoms, compared with how they were before the study intervention, on a 7 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." 'Success' is defined as responses of 'very much improved' or 'much improved'; this will capture whether the women are satisfied with their treatment.

The primary economic outcome is the incremental cost per quality adjusted life year (QALY) gained of urodynamics and comprehensive clinical assessment compared to comprehensive clinical assessment only, modelled over the lifetime of the patients.

5.2 *S*econdary outcome measures

- A less strict definition of success at 15 months derived from the PGI-I where success is defined as a response of "very much improved", "much improved" or "improved".
- Proportion of women receiving invasive treatment at 6 and 15 months post-randomisation;
- Participant reported outcomes at 3, 6 and 15 months post-randomisation including:
  - OAB symptoms measured by the ICIQ-OAB and UPS;
  - Urgency and UUI episodes measured using the bladder diary;
  - Other urinary symptoms measured using the 3 domains of the ICIQ-FLUTS (filling, voiding and incontinence) and the bladder Diary;
  - Generic health related QoL status measured using general (EQ-5D-5L) and condition specific (ICIQ-LUTSqol) QoL assessment tools.
- Adverse Events:
  - All serious adverse events (SAE – section 7.1);

- UTI requiring antibiotic treatment;
- For subsequent treatments:
    - BoNT-A treatment: urinary retention requiring clinical intervention (e.g. catheterisation); clean intermittent self-catheterisation (CISC).
    - SNM: Infection of the SNM lead; lead migration, revision of surgery; wound infection.
    - SUI surgery: Bladder injury; intra operative bleeding requiring return to theatre; post-operative wound infection; nerve injury; tape exposure/extrusion into vagina/ lower urinary tract; tape excision/ division; tape infection; new onset and related pelvic pain; urinary retention requiring intervention (e.g. catheterisation); clean intermittent self-catheterisation (CISC); others.

- Qualitative study outcomes:
    - Participants' attitudes to invasive testing and expected outcomes (prior to randomisation or knowing their allocated study group);
    - Participants' attitudes to potential treatment options (prior to randomisation or knowing their allocated study group);
    - Participants' experience of urodynamics and opinions regarding treatment outcome to include evaluation of treatment satisfaction or desire for further treatment (3 to 6 months post-treatment;
    - Surgeon attitudes to the influence of urodynamics on decision making (at start of the study and 6 to12 months after starting recruitment at their sites).

- **Secondary economic outcomes include;**
    - Incremental cost per QALY gained of urodynamics and comprehensive clinical assessment compared to comprehensive clinical assessment only up to 15 months;
    - Incremental cost per QALY gained of BoNT-A vs SNM as the initial treatment for refractory OAB over the lifetime of patients;
    - Incremental cost per QALY gained of SNM test and BoNT-A treatment according to clinical assessment only compared to treatment guided by urodynamics over the lifetime of patients;
    - Expected value of perfect information and associated partial values over the lifetime of patients.

6. DATA COLLECTION AND PROCESSING

6.1 Measuring outcomes

Table 1: Source and timing of measures

Outcome measure	Source	Timing			
		Baseline*	Post-randomisation (months)		
			3	6	15
Treatment success PGI-I	PQ		✓	✓	✓
Generic Health status	PQ	✓	✓	✓	✓
EQ-5D-5L					
Condition specific quality of life	PQ	✓		✓	✓
ICIQ-LUTSqol					
Urinary symptoms	PQ	✓	✓	✓	✓
ICIQ-OAB					
ICIQ-FLUTS UPS: Urgency Perception Scale					
Urgency and Urgency Urinary Incontinence episodes on (3 day bladder diary)	PQ	✓		✓	✓
Bladder scan	CRF	✓			
Interventions received	CRF, PQ		✓	✓	✓
Adverse events	CRF, PQ		✓	✓	✓
NHS primary and secondary healthcare use	CRF, PQ	✓		✓	✓
Participant resource use	PQ	✓		✓	✓

CRF = case report form, PQ = participant completed questionnaire
*Baseline is after informed consent has been given but prior to randomisation

We are measuring treatment success (PGI-I), health status (EQ-5D-5L), urinary symptoms (ICIQ-OAB and UPS), interventions received and adverse events (UTIs requiring antibiotics treatment) at 3 months post-randomisation (which is approximately the time of completion of the interventions).

We are measuring all other participants reported outcomes at 6 and 15 months post-randomisation which is expected to be approximately 3 and 12 months post-treatment. These two timings are appropriate for measuring the outcomes of treatments for refractory OAB. Six months post-randomisation is adequate to capture the participants reported and objective outcomes and early adverse events for each treatment, while the 15 months post-randomisation is appropriate to compare the post intervention overall outcomes (participants reported/ objective success rates, patient satisfaction, adverse events, further treatment, cost utility and cost-effectiveness) between the study groups.

6.2 Baseline data collected will include:

- Participants' demographics: Age, Parity; BMI; Smoking; Body Mass Index
- Clinical Diagnosis: OAB vs Urgency predominant MUI
- Number of confirmed episodes of urinary tract infections (UTIs) in the past 12 months; patients using CISC and/or on prophylactic low dose antibiotics.
- Previous treatments received for urinary incontinence and OAB including PFMT; bladder retraining; biofeedback; percutaneous tibial nerve stimulation; pharmacological treatment; invasive treatments such as surgery for SUI and others.
- Participants' Questionnaires: The International Consultation on Incontinence Questionnaire - Female Lower Urinary Tract Symptoms(ICIQ-FLUTS), Urgency Perception Scale(UPS),

The International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB); The International Consultation on Incontinence Questionnaire – Lower urinary tract symptoms Quality of Life (ICIQ-LUTSqol); and EQ-5D-5L.

6.3 Intervention Data to be collected:

6.3.1. Comprehensive Clinical Assessment Data Collected (CRF):

- Detailed history:
    - Assessment of urinary symptoms including storage, filling and incontinence symptoms. The most bothersome urinary symptoms.
    - Previous investigation and/ or treatment (conservative, pharmacological and or surgical) for UI and OAB.
    - Past medical or surgical history of relevance.

- Clinical examination:
    - Stress urinary incontinence
    - Pelvic organ prolapse
    - Pelvic masses and other pelvic pathology

- Non-invasive clinical assessments:
    - Bladder Diary for 3 days to assess daytime frequency; nocturia; urgency and UUI episodes (N.B. A minimum of 24 hours completed diary will be accepted as valid diary. Diary completed at a previous clinic visit within last 3 month will be accepted)
    - Post-voiding residual urine volume using ultrasound bladder scanning (and/or non-invasive free uroflowmetry if performed).

- Clinical diagnosis: OAB versus MUI.

6.3.2. Urodynamics Data Collected (CRF):

- Bladder Diary (as above).
- Urodynamics diagnosis (DO/ MUI/ USI/ others)
- Voiding assessment on free uroflowmetry:
    - Voided Volume
    - Post-voiding residual urine volume
    - Pattern: Normal/ Obstructed/ Equivocal/ Abdominally Assisted/ others
    - Maximum Flow Rate and Average flow rate
- Voiding assessment on pressure flow studies (if performed) – same data as uroflowmetry
- Maximum urethral closure pressure on urethral pressure profile (if performed)

6.4. Follow up

- At 3 months post-randomisation, participants are asked to complete the PGI-I; interventions received; urinary symptoms (ICIQ-OAB and UPS); EQ-5D-5L and any AE.

- At 6 and 15 month post-randomisation, participants are asked to complete the PGI-I; intervention(s) received; and in addition, completion of validated symptom severity and QoL questionnaires: ICIQ-FLUTS; ICIQ-OAB; ICIQ-LUTSqol; UPS; and EQ-5D-5L and a 3 days bladder diary (Fig 1- Study Flow Chart).

We offer and use all methods of delivery and collection of questionnaires and reminders including use of research teams for time points associated with hospitalisation, post, e-mail, web based and SMS text, taking into account each participant's stated preferred means of receiving and completing the measures(recorded on the participant contact preference form).

Up to three reminders will be sent to participants by post, email, phone or text message, taking into account any preferences they may have for mode of communication.

A small token of appreciation (gift voucher(s) of modest value up to £15) will be sent to participants on receiving their completed follow up questionnaires), unless they opt out on the study consent form.

- At 6 and 15 months post-randomisation; the local research team will review the clinical health records and complete the relevant CRF for the following data:
    - Data in section 6.3;
    - Initial treatment received by the participants following the trial intervention and its details: Date and type of treatment/ type of anaesthesia/ immediate AE/ number of subsequent hospital admissions for this treatment episode (such as voiding assessments/ CISC management/ adjusting SNM, others);
    - Subsequent outpatient clinic visits;
    - Any subsequent relevant investigations or treatments;
    - Adverse events (please see safety section for expected related AE).

6.5 Data processing

The local research team enter locally collected data in the centres. Staff in the Trial office will work closely with local research teams to ensure the data are as complete and accurate as possible.

Follow-up questionnaires to participants are sent from and returned to the Trial Office in Aberdeen. Extensive range and consistency checks are designed to further enhance the quality of the data.

6.6 Change of Status/Withdrawal procedures

Participants are free to withdraw consent to participate at any time. All changes in status (with the exception of complete withdrawal of consent) mean the participant is followed up for the trial outcomes wherever possible. Participants who do not receive their allocated intervention, either because of participant preference or change of circumstance will not result in withdrawal and the participant will continue to participate as per trial follow up schedule unless the participant declines trial follow up.

Participants who wish to withdraw from the trial follow-up are encouraged to allow routine follow up data from hospitals to be used for trial purposes. We will adhere to the wishes of the participants.

All data collected up to the point of complete withdrawal are retained and used in the analysis. Participants who do not complete their follow up but for whom any outcome data are available will be included in an intention to treat analysis.

6.7 Long term follow-up

We plan to seek funding and the necessary approvals to follow up participants in the longer-term using participants' questionnaires; data from NHS and other government central registries; and GP and hospital records. The PIL informs the participants of this proposal and we seek participants' consent at the outset of the study to be contacted (or not) for long term follow up.

7. SAFETY

Urodynamics investigation is recommended by the NICE guidelines for assessment of women with refractory OAB however with no robust evidence to show its superiority over the comprehensive clinical assessment only. Urodynamics can have AE such as discomfort, embarrassment, and anxiety during the procedure and lower UTI within the following few days. This trial compares undertaking urodynamics investigation and comprehensive clinical assessment versus comprehensive clinical assessment only hence there should not be any additional risks for this cohort of women by participating in the study. Nevertheless, by

participating in the study, it is possible that more women in the comprehensive clinical assessment arm only will be offered treatments; the latter is one of the outcomes of the study.

7.1 Standard Definitions

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Adverse events are not:

- continuous and persistent disease or symptom, present before the trial, which fails to progress;
- signs or symptoms of the disease being studied; or
- treatment failure.

A **serious adverse event** (SAE), is any AE that:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- results in persistent or significant disability or incapacity;
- requires hospitalisation or prolongation of existing hospitalisation;
- is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition is not considered as an AE or SAE.

In the FUTURE study planned hospitalisations for receiving treatment within the defined treatment pathways (such as SNM, Botulinum toxin injection, others) and their relevant readmissions (such as for voiding assessments, teaching CISC, urinary retention) are not recorded as SAE but are collected within the study outcomes.

FUTURE Study related expected adverse events

In this trial the following AE are potentially expected:

- Urodynamics: Urinary tract infection requiring antibiotic treatment; fainting, transient worsening of symptoms, discomfort, embarrassment and anxiety.
- BoNT A treatment: UTI requiring antibiotic treatment, urinary retention requiring intervention (e.g. catheterisation); CISC; haematuria; limb weakness, paralysis.
- SNM: Infection of the SNM lead; lead migration, revision of surgery; wound infection; pain.
- SUI surgery: Bladder injury, bowel injury, intra operative bleeding requiring blood transfusion and/or return to theatre; post-operative wound infection; nerve injury; recurrent UTI requiring antibiotic treatment; tape exposure into the vagina/ lower urinary tract; tape excision/ division; tape infection; new onset pelvic pain or worsening of existing pain; urinary retention requiring intervention (e.g. catheterisation); CISC.
- Anaesthesia related AE.
- Drug reactions such as for Antibiotics; local/ general anaesthesia.

7.2 Trial specific considerations

In this trial, all related AEs will be recorded (see definition of “related” in section 7.3.3 below). All serious related AEs will be recorded as SAEs. All deaths (any cause) will also be recorded as SAEs

7.3 Procedures for detecting, recording, evaluating & reporting AEs, SAEs

7.3.1 Detecting AEs and SAEs

All AEs and SAEs meeting the criteria for recording within the trial (see section 7.2) are recorded from the time a participant consents to join the trial until the end of their follow up period.

Every follow-up visit and questionnaire will inquire on expected AEs/SAEs. In addition, open ended and non-leading verbal questioning of the participant will also be used to enquire about AE/SAE occurrence or re admission to hospital and any further treatment received.

7.3.2 Recording AEs and SAEs

Depending on severity, when an AE/SAE meeting the criteria for recording within the FUTURE Study occurs, it is the responsibility of the local PI (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The PI or delegate should then record all relevant information in the CRF (and on the SAE form if required).

Information collected includes type of event, onset date, PI or delegate assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

7.3.3 Evaluating AEs and SAEs

Seriousness, relatedness (causality), and expectedness are evaluated.

Assessment of Seriousness*:* The PI or delegate will make an assessment of seriousness as defined above.

Assessment of Relatedness (causality)*:* The PI or delegate will make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- **Related**: resulted from administration of any of the research procedures i.e. study intervention or subsequent treatments.
- **Unrelated**: where an event is not considered to have resulted from any of the research procedures.

Alternative causes such as natural progression of the underlying pathology, concomitant therapy, other risk factors and the temporal relationship of the event to the intervention are considered.

Assessment of Expectedness: When assessing expectedness refer to the expected events (Section 7.1).

7.3.4 Reporting AEs and SAEs

PI or delegates are responsible for notifying the trial office of any SAEs that require to be recorded in line with the FUTURE study protocol. If an SAE is recorded on a participant questionnaire, the Trial office liaises with the relevant study site to obtain further information

When an SAE form is uploaded onto the trial website, the Trial Manager is automatically notified. If, in the opinion of the local PI and/or the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager notifies the sponsor within 24 hours of receiving the signed SAE notification. The sponsor provides an assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity is resolved by further discussion between these parties.

The CI or delegate reports any related and unexpected SAEs to the REC within 15 days of the CI becoming aware of it.

If all the required information is not available at the time of reporting, the PI or delegate must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow up information of a previously reported event.

7.3.5 Regulatory reporting requirements

The CI or delegate is responsible for submitting annual reports to the REC and Sponsor on the anniversary of the approval.

8. SAMPLE SIZE AND PROPOSED RECRUITMENT RATE

8.1 Sample size

The sample size calculation is more challenging than usual, since the potential benefit of urodynamics, if any, is to select the most appropriate treatment, rather than being a treatment itself.

Survey of the potentially collaborating units showed that in clinical practice, the majority of 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*. (2011) and Chapple *et al.* (2013) both showed a success rate of around 60% in women with refractory OAB without the urodynamics diagnosis of DO.[14,16] These two studies defined success differently: Chapple *et al.* assessed patient-reported success at 12 weeks following injection of 100 units BoNT-A and defined success as greatly improved or improved;[16] 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.[14]

We have also established a consensus amongst clinicians and patient and public involvement groups (PPI) that for urodynamics to be worthwhile, it will need to demonstrate a minimum of 10% superiority over comprehensive clinical assessment only. For 90% power and a 5% level of significance, 986 participants (493/ group) are needed using a chi-squared test with continuity correction,[37,38] rising to 1096 (or 548/group) to allow for 10% attrition at 15 months-post-randomisation.

8.2 Recruitment rates

We performed a detailed survey of practice for all potentially collaborating units and the results suggested a wide range of eligible participants (n= 8-20) per month. We based our original recruitment projection on a conservative estimate of 38 centres (each recruiting 2.2 per month per centre) to achieve our target of 1096 participants over the 20 month recruitment period. The 20 month recruitment period allowed for a staggered site set up and 50% lower recruitment during peak holiday times (Easter, Christmas, and summer).

However, due to the lower than predicted recruitment rate, a 12 month extension to the recruitment phase is required. The revised recruitment projections for the extension period are based on a conservative estimate of the recruitment trend over the last eight month period from June 2018 to January 2019. This resulting in an expected recruitment rate of 44 participants per month, with an expected 50% lower recruitment rate during peak holiday times.

An additional six month extension to the recruitment end date is necessary to account for the pause in recruitment due to the COVID-19 pandemic (new recruitment end date 30th November 2020). This was further extended to the end of January 2021. These projections may be further revised depending on the time required for sites to restart research activities (see Appendix 3). It is anticipated that not all sites will be able to restart during the short extension period which is dependent on resumption of clinical services relevant to the study procedures and overall capacity to deliver the study in terms of research nurse support.

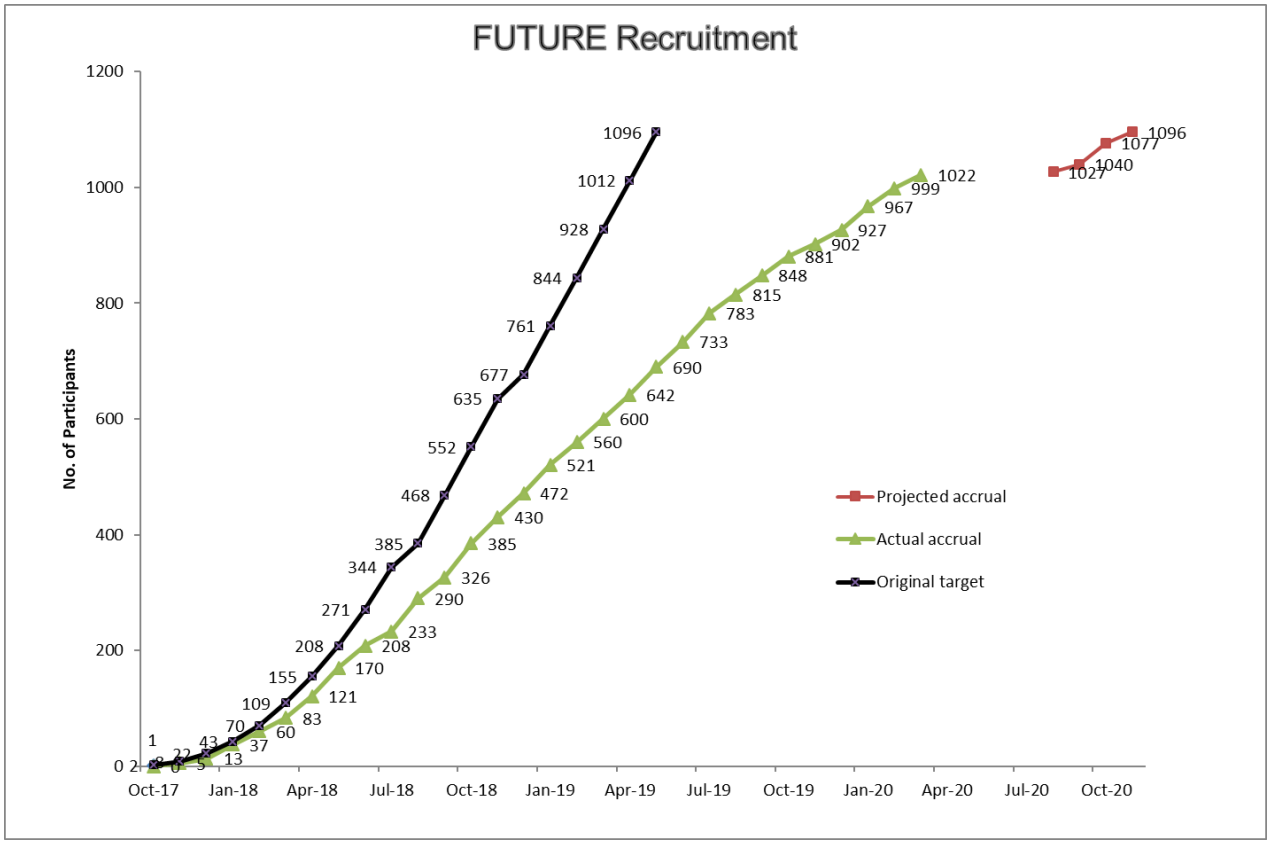

Figure 2: Projected participant recruitment

8.2 Project timetable and milestones

The study starts on 1st May 2017 and the duration is 63 months including an internal pilot phase:

Months: 1-5: study initiation, NHS approvals; start site set up;
Months: 6-16: staggered site start up; establish study in 38 centres;
Months: 6-37: identify and recruit participants;
Months: 26-54: complete 15 months follow up;
Months: 45-63: close down, analysis, report writing.

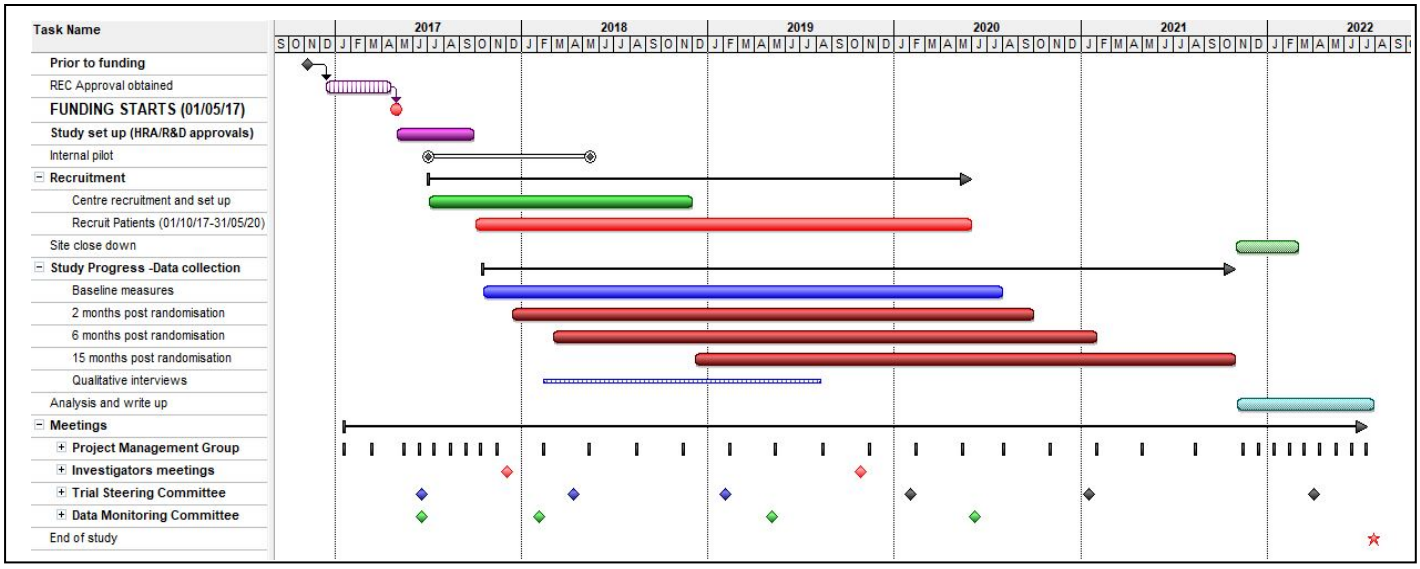

Figure 3: FUTURE study Gantt Chart

8.3 Internal pilot study

The internal pilot study with stop/go criteria is designed to establish whether the projected recruitment rate is achievable. By the middle of calendar month 13 (recruitment month 8) we will have 20 sites open and should have achieved at least 66 centre months of recruitment, or around 145 randomised (the target sample size is 1096 over ~500 centre months, which gives an average of 2.2 per centre month).

1. If recruitment is no more than 2 standard deviations (SD) below the expected number, recruitment continues without modification.
2. If recruitment is between 2 and 4 SD below the expected number, the recruitment approach will need to be modified. This could be recruiting more centres or allowing for more recruitment time at a centre by either setting up faster or lengthening the recruitment period at the best recruiting centres. In this instance recruitment would continue to be monitored to ensure that the modifications had worked.
3. If recruitment is more than 4 SD below the expected number, the expected number is not achievable and discussions would be entered into on whether the RCT is feasible with the possibility that the trial would need to be terminated.

In the pilot phase, we are also monitoring:

- Timelines from randomisation to receiving the intervention and receiving the treatment.
- Patterns of deviations from the treatments offered within the treatment pathways (e.g. patient with diagnosis of OAB but receiving SUI surgery).
- Return rate of questionnaires and bladder diary.

9. STATISTICAL ANALYSIS

9.1 Analysis Plan

Primary and secondary outcomes are compared using generalised linear models, with adjustment for the minimisation covariates (centre and diagnosis of OAB versus MUI). Sensitivity analyses are used to explore additional adjustment of healthcare professional effects which arise from a better diagnosis being made due to the use of urodynamics. This is similar to adjusting for surgeon effects when there is more than one surgeon within a centre.

The primary outcome is participant reported success as measured by the PGI-I at 15 months post-randomisation (approximately 12 month post-treatment). For the primary analysis, the PGI-I responses are dichotomised to ‘success’ defined as ‘very much improved’ or ‘much improved’ and the rest of responses defined as failures as this is felt to be the best categorisation of whether the women are satisfied with their treatments and interventions. We use a repeated measures mixed effects logistic regression, including the 6 month measurement to increase the power to estimate the treatment effect at 15 months post-randomisation.

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

In addition, we perform a secondary supporting analysis using ordinal logistic regression on the 7-point PGI-I scale. This will also use a generalised ordered logit model with the partial proportional odds model (for example, as implemented in ‘gologit2’ in Stata) to relax this restrictive assumption of the full proportional odds model.

The statistical analysis of the primary outcome will utilise the usual intention to treat (ITT) – or “intention to diagnose”. We also include a suitably defined per protocol (PP) analysis as a secondary supporting analysis.

We assess how robust all findings are to any missing data (anticipated to be no more than 10% for the primary outcome) using multiple imputation approaches under an assumption of missing at random. We consider non-ignorable missing data mechanisms if the patterns of missing data across the two randomised groups suggests this is appropriate.

We specify the statistical techniques for these long term follow up data (generally, just extensions of the within trial analyses above) in the full Statistical Analysis Plan, authored by the study statistician and agreed by the Trials Steering Committee and independent Data Monitoring Committee.

9.2 Planned subgroup analyses

As above, we compare the outcomes in pre-specified subgroup of participants with OAB vs MUI

In addition, we will explore, in a non-randomised analysis, the:

1. Clinical and cost effectiveness of the different treatment pathways of those initiated on BoNT-A treatment vs those initiated on SNM treatment.
2. Clinical and cost effectiveness of SNM treatment according to clinical assessment only compared to treatment guided by urodynamics.
3. Clinical and cost effectiveness of BoNT-A treatment according to clinical assessment only compared to treatment guided by urodynamics

9.3 Proposed frequency of analyses

One definitive analysis will be performed at end of the follow up phase (i.e. no interim analysis).

10. ECONOMIC EVALUATION

The economic evaluation is from an NHS perspective, using both a within trial timeframe and a modelled patient lifetime timeframe. The modelled analysis is the primary focus of the economic sub study. Unit costs will be taken from standard sources (NHS Reference Costs, British National Formulary and 'Unit Costs of Health and Social Care'). Costs and outcomes are discounted at 3.5%.

10.1 NHS Health Service Resource Use

Patient level data are collected for the study interventions: urodynamics and comprehensive clinical assessment versus comprehensive clinical assessment only, plus subsequent treatments, investigations and other health service contacts. Data are collected at 6 and 15 months post-randomisation (3 month and 12 month post-treatment) via a review of patient medical records. These data are entered onto the study database at these points. Primary care contacts are collected via patient questionnaires.

10.2 Non NHS resource use

Other related care contacts funded outside the NHS are not anticipated.

10.3 Patient costs

The costs to patients of undergoing treatment and personal expenditure on products relating to their symptoms related to OAB are captured by a questionnaire at baseline, 6 and 15 months.

10.4 Other costs

Wider societal costs are collected from the patient. Such costs include time taken away from normal activities due to treatment or symptoms, including time taken off work due to treatment of symptoms. Reduced productivity at work due to symptoms are also recorded. These data are collected using the same questionnaires as described in Section 10.3.

10.5 Quality adjusted life years

Health related utility is assessed using the EQ-5D-5L measure at baseline; at intervention stage (i.e. urodynamics); and at 6 months and 15 months post-randomisation.

QALYs will be estimated using the EQ-5D-5L tariff that is recommended by NICE at the time of the analysis; this is currently the van Hout 'cross-walk' tariff.[39] . QALYs are estimated using linear interpolation between time points. Exploratory analysis will be 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 3 months post-randomisation are affected by time since urodynamic testing. If a robust estimate of QALY loss is produced, then sensitivity analysis will examine the impact of its incorporation into the cost-effectiveness analysis.

10.6 Within trial cost effectiveness analysis

The within trial analysis follow the best practice guidelines.[40] The analysis calculate total costs and quality adjusted life years (QALYs) for each patient and estimate the incremental costs and QALYs using a seemingly unrelated regression model with baseline covariates including age and baseline EQ-5D-5L score and missing data imputed using multiple imputation.[41,42]

The cost effectiveness acceptability curves will be based on the adjusted and imputed analysis described above. . Deterministic sensitivity analyses are undertaken to look at three sources of methodological uncertainty; societal perspective, the EQ-5D-5L tariff and any QALY loss associated with urodynamics identified in the exploratory analysis described above. Undertaking a sensitivity analysis with the EQ-5D-5L tariff is required as alternative tariffs are available; the current recommended tariff is the van Hout 'cross-walk' tariff..[43]

10.7 Patient lifetime cost-effectiveness analysis

The primary analysis is model based. Such an approach is considered superior to trial based analyses as it can be designed to better fit the research question and incorporate other relevant sources of data.[44] In this particular situation, the model can incorporate the longer term costs and consequence of using urodynamics which cannot be observed in the trial. However, the first 15 months of the model will be based on the trial results. The structure of the model beyond 15 months will be based on a pre-existing model.[18] A key improvement over this model is the use of more appropriate utilities taken from the trial. In addition, targeted literature searches are undertaken to assess whether any relevant new studies have been published for the other parameters.

In line with Rachaneni model,[18] exploratory analyses examine whether targeted urodynamics for a sub group of patients has the potential to be cost effective. In addition to Rachaneni, we undertake two exploratory analyses:

- A non-randomised comparison of the cost-effectiveness of different sequence of treatments (i.e. initiated on BoNT-A vs SNM).
- A non-randomised comparison of the cost-effectiveness of SNM according to clinical assessment only compared to treatment guided by urodynamics.

These two comparisons take account of the lack of randomisation using methods consistent with those of the analogous clinical analyses.

A probabilistic sensitivity analysis will be undertaken on the modelled results and its associated incremental cost-effectiveness ratio, cost effectiveness plane and cost-effectiveness acceptability curves generated. Value of information analysis will be undertaken using SAVI (http://savi.shef.ac.uk/SAVI/). The partial values are used to identify those parameters where there is greatest value in resolving outstanding uncertainty. Deterministic sensitivity analyses will bw undertaken to look at the three sources of methodological uncertainty; societal perspective, the EQ-5D-5L tariff and the length of disutility associated with urodynamics.

11. QUALITATIVE RESEARCH

Aims: A qualitative component is included within the study to evaluate the patients' attitudes to, and experiences of, invasive urodynamic testing, and also clinicians' views on the influence of urodynamics on decision-making.

The four main aims of the qualitative work package are to explore:

1) Participants' attitudes to invasive testing and expected outcomes (prior to randomisation or knowing their allocated study group);
2) Participants' attitudes to potential treatment options (prior to randomisation or knowing their allocated study group);
3) Participants' experience of urodynamics and opinions regarding treatment outcome to include evaluation of treatment satisfaction or desire for further treatment (3 to 6 months post-treatment). We aim to capture the same group who underwent interviews prior to randomisation however we will have scope to widen the group to achieve data saturation as needed;
4) Surgeon attitudes to the influence of urodynamics on decision making (at start of the study/ 6 to 12 months after starting recruitment at their sites).

Methods: A standardised approach is employed to explore the above areas in accordance with published qualitative research methods.[45-49]

Participants who consent to the qualitative research will be sent a dedicated PIL for the qualitative study interviews. This will be followed by an email and/or phone call from a qualitative team researcher to answer any of the participants' queries. Verbal consent is received by the Researcher when the interview is conducted.

Face to face participants' interviews are conducted where possible with telephone interviews included for remote study sites, and carried out by an experienced qualitative researcher. Interviews are semi-structured and follow a topic guide informed by literature review and discussion between study researchers, and encourage participants to discuss their perspectives with regard to the aims above (pre randomisation and 3 to 6 months post-treatment). Interviews are audio recorded, transcribed verbatim (including descriptions of non-verbal factors where appropriate) and uploaded onto a qualitative software package (QSR Nvivo 10) to aid data management. Analyses are conducted by the qualitative researcher according to principles of thematic content analysis.

Recordings are listened to and transcripts read and re read for familiarisation. Segments of text are 'coded' by assigning descriptive labels. Codes are grouped on the basis of shared properties to create themes and coded transcripts are then examined and compared to inductively refine and delineate themes (constant comparison). A subset of interviews are independently analysed by a second study researcher and coding discrepancies discussed to maximise rigour and reliability. Plausibility of data interpretation are further discussed between the study team throughout the analyses. Descriptive summary accounts of the audio recordings and interviews are prepared.

Theoretical purposive (non-probability) sampling is used to ensure the diverse characteristics of the population are sampled (e.g. participants varying in age and relevant clinical history). MUI vs OAB, investigations received: urodynamics and comprehensive clinical assessment versus comprehensive clinical assessment only, and treatments received: SNM vs. BoNT to include day case vs. local anaesthetic procedures). Sampling and analyses continues in iterative cycles until data saturation is achieved. It is anticipated a minimum of thirty to forty patient interviews will be undertaken to effectively capture the opinions of those in both arms of randomisation, the numerous potential treatments, and treatment considered successful and failed. Approximately ten to fifteen clinician interviews are proposed to explore the clinical aspects of urodynamics with regard to clinical decision making.

12. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 Trial office in Aberdeen

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager takes responsibility for the day to day transaction of trial activities, for example approvals, site set up and training, oversight of recruitment and follow up rates etc. The Data Co-ordinator provides clerical support to the trial, including organising all aspects of the questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal).

The FUTURE Trial Office Team (CI, trial manager, data coordinator, statistician) meets formally, approximately fortnightly during the course of the study to ensure smooth running and trouble-shooting, but more frequently during the set up phase as required.

12.2 Local organisation in sites

Hub Structure: Each of the hubs has a number of centres attached and is led by a hub leader/ grant holder and a part time hub co-ordinator. The hub leader and co-ordinator support the trial manager/ office with the set-up of their centres; ensure continuous engagement of their PIs and research nurse;, and promote recruitment within their hubs.

The PI and research nurse(s) in each site are responsible for all aspects of local organisation including identifying potential recruits, consenting, assessing participants and, completing and maintaining appropriate documentation. The site agreement documents the full list of responsibilities for sites. Appropriate members of the local team are knowledgeable about the Protocol and will have appropriate Good Clinical Practice (GCP) training if applicable. A study specific Delegation Log is prepared for each site, detailing the responsibilities of each member of staff working on the study. The local team is also responsible for notifying SAEs to the trial office (see section 7).

12.3 Project Management Group (PMG)

The trial is supervised by its Project Management Group (PMG). The group consists of grant holders and representatives from the Trial Office. Observers are invited to attend at the discretion of the PMG. The PMG meets approximately every 2 months in the first and last six months of the trial and approximately every 3 months in-between.

The PMG has the expertise to cover the clinical, methodological and management aspects of the FUTURE study.

Any modification to the project is normally discussed by the PMG, and when relevant by the TSC, and is approved by the Sponsors and funder before application to REC and R&D. An exception to the above is in the case where an immediate implementation of safety measures is required; the Sponsor is then notified as soon as possible.

12.4 Independent Trial Steering Committee (TSC)

A Trial Steering Committee (TSC), with independent members oversees the conduct and progress of the FUTURE study. The TSC Charter documents the terms of reference of the TSC, the template for reporting and details the membership with names and contact details of the TSC. This Charter is filed in the Trial Master File (TMF).

12.5 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) oversees the safety of participants in the FUTURE study. The DMC Charter documents the terms of reference of the DMC and the names and contact details. This is filed in the Trial Master File. The committee meets every six to twelve months to monitor the study data and make recommendations as to any

modifications that are required to be made to the protocol or the termination of all or part of the study. CHaRT has adopted the DAMOCLES Charter for DMCs.[50]

12.6 Patient and Public Involvement (PPI)

The trial team established collaboration and partnership with the largest relevant patient support groups in the UK:

- The Bowel and Bladder Foundation (B&BF), the largest relevant patient centred organisation in the UK at time of the study design, participated in the development of the full study proposal. Based on its wide patient involvement and considerable expertise in this field, B&BF advised on the patients' perspectives for the study design, treatment pathways and the proposed assessment tools and outcome measures at time of study design.
- Bladder Health UK (previously the Cystitis and Overactive Bladder (COB) Foundation) is a grant holder and part of the PMG. Bladder health UK provides a clear leadership on the patient perspective in the FUTURE study and is integral to the development of the study protocol and all the study documents including the PIL; participants' letter of invitation/ reminders; participants' questionnaires, and bladder diary.

Bladder Health UK (study PPI) will contribute to the final HTA monograph and development of its plain language summary and dissemination on their websites and other relevant societies.

13. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

13.1 Research Governance

CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs. The trial is run under the auspices of CHaRT based at HSRU, University of Aberdeen. This aids compliance with Research Governance, and the principles of GCP and provides centralised trial administration, database support and statistical analyses.

The CI/ PMG ensures, through the TSC and Sponsor that adequate systems are in place for monitoring the quality of the trial (compliance with appropriate governance) and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial. CHaRT's Standard Operating Procedures (SOPs) are followed.

13.2 Data protection

Data collected during the course of the research is kept strictly confidential and accessed only by members of the trial team and may be looked at by individuals from the Sponsor organisation or NHS sites for the purposes of monitoring and audit.

Participants are allocated a unique Study Number. Participant's details are stored on a secure database under the guidelines of the 1998 Data Protection Act. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired. The CHaRT senior IT manager (in collaboration with the CI) manages access rights to the data set. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta analyses.

13.3 Sponsorship

The University of Aberdeen and Grampian Health Board (NHS Grampian) are the co sponsors for the trial.

14. ETHICS AND REGULATORY APPROVALS

The North of Scotland Research Ethics Committee reviewed this trial. The trial is conducted according to the principles of GCP provided by Research Governance Guidelines. Annual progress reports, end of trial declaration, and a final report are submitted to the Sponsor and the North of Scotland REC within the timelines defined in the regulations.

14.1 Protocol compliance and amendment

The Investigators will conduct the study in compliance with the Protocol given approval / favourable opinion by the Ethics Committee. Any amendments to the project are approved by the Sponsors and funder before application to REC and R&D unless in the case of immediate safety measures being required/ implemented when the Sponsor is notified as soon as possible. Any deviations from the Protocol will be fully documented.

15. QUALITY ASSURANCE

The trial is monitored to ensure that it is being conducted as per protocol, adhering to Research Governance, the principles of GCP, and all other appropriate regulations. The approach to, and extent of monitoring are specified in a trial monitoring plan and is appropriate to the risk assessment of the trial. PIs and their host Trusts are required to permit trial related monitoring and audits to take place by the Sponsor and/ or regulatory representatives providing direct access to source data and documents as requested.

15.1 Risk assessment

An independent risk assessment has been carried out by the sponsor and any amendment will be reviewed against the original risk assessment.

16. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the National Institute for Health Research, Health Technology Assessment programme (NIHR HTA).

The necessary trial insurance is provided by the Sponsor - University of Aberdeen.

17. END OF TRIAL

The end of follow up for each participant is defined as the final data capture on that individual. The end of the trial is defined as the end of funding.

The end of the trial is reported to the REC and Sponsor within 90 days, or 15 days if the trial is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the trial is provided to the REC within one year of the end of the trial. An end of trial report is also issued to the funders at the end of funding.

18. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data including questionnaires/ diaries, etc, are entered into the FUTURE study database by the local PI and/or local research teams working in each hospital site. Questionnaires/ diaries, etc returned by post to the trial office are entered there. Staff in the trial office works closely with local research teams to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks are designed to further enhance the quality of the data.

Responsibilities for archiving are documented in the co-sponsorship agreement. All essential data and documents (electronic and hard copy) are retained for a period of at least 10 years after close of trial according to the relevant UoA/NHSG Sponsor and CHaRT archiving SOPs. Electronic data are archived by CHaRT.

19. SATELLITE STUDIES

It is recognised that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these are discussed in advance with the Project Management Group, and if appropriate with the Trial Steering Committee. Depending on the nature of the satellite study, the Sponsor may consider this to be a non substantial or a substantial amendment to the REC approval, or to require REC approval as a project in its own right. R&D management approval may also be required.

20. AUTHORSHIP AND PUBLICATION

All RCTs have a commitment to publish the findings of the research. At a minimum this trial will have a results paper published in a peer reviewed medical/scientific journal.

All grant holders and research staff who fulfil authorship criteria as detailed in the ICMJE http://www.icmje.org/recommendations/browse/ should be named in the by line of the paper i.e. Jane Doe, John Doe, John Smith and Ann Other.

However, there may be situations where this is not possible, for example if the journal limits the number of authors. In such circumstances group authorship may be appropriate using by lines similar to “CI and The FUTURE trial group” or “Jane Doe, John Doe, John Smith, Ann Other and the FUTURE trial group”. The article should carry a footnote of the names of the people (and their institutions) represented by the corporate title.

For reports which specifically arise from the trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to “the named individual(s) for the FUTURE Trial Group”.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the PMG.

We maintain interest in the trial by publication of the FUTURE study newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent e.g. in a final FUTURE Newsletter to all involved in the trial. Further details on the publication policy can be found in Appendix 2.

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APPENDICES

Appendix 1: FUTURE Study Flow Diagram and Treatment Pathways

Appendix 2: CHaRT Publication Policy

Appendix 3: Implications of COVID-19 pandemic