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INVESTIGATE-I (**INV**asive **E**valuation before **S**urgical **T**reatment of **I**ncontinence **G**ives **A**dded **T**herapeutic **E**ffect?): a pragmatic multicentre pilot study to assess the feasibility of a future randomised controlled trial

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3. KEYWORDS

Feasibility; pilot studies; randomised controlled trial; pragmatic trials; qualitative studies; urodynamics; stress urinary incontinence; surgery

4. GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BAUS	British Association of Urological Surgeons
BAUS-SFNUU	BAUS Section of Female, Neurological and Urodynamic Urology
BSUG	British Society of Urogynaecology
CI	Chief Investigator
CRF	Case Report Form
DMEC	Data Monitoring & Ethics Committee
DO	Detrusor Overactivity
eSAE CRF	Electronic Serious Adverse Event Case Report Form
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICI	International Consultations on Incontinence
ICIQ	ICI modular Questionnaires
ICIQ-FLUTS	ICIQ Female Lower Urinary Tract Symptoms questionnaire
ICIQ-LUTSqol	ICIQ Lower Urinary Tract Symptoms Quality of Life questionnaire
ICIQ-UI SF	ICIQ Urinary Incontinence Short Form questionnaire
IMP	Investigational Medicinal Product
IUT	Invasive urodynamic tests
MREC	Main Research Ethics Committee
MUI	Mixed urinary incontinence
NCTU	Newcastle Clinical Trials Unit
NIHR	National Institute for Health Research
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NRES	National Research Ethics Service
PFMT	Pelvic Floor Muscle Training
PGI-I	Patient Global Impression of Improvement
PI	Principal Investigator (at each site)
POP	Pelvic Organ Prolapse
PROM	Patient Reported Outcome Measure
QALY	Quality Adjusted Life Year
QOL	Quality of Life
R&D	Research and Development
SAE	Serious Adverse Event
SUI	Stress Urinary Incontinence
TSC	Trial Steering Committee
UDI	Urogenital Distress Inventory
UI	Urinary incontinence
UUI	Urge urinary incontinence

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6. PROTOCOL SIGNATURE PAGE

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Prof Luke Vale, Health Economist

Signature ……. Date…….
Mr Chris Speed, Senior Trial Manager

6.2. LOCAL PRINCIPAL INVESTIGATOR SIGNATURE

I confirm that I have read and understood protocol version 1.1 dated 01.07.11 I agree to comply with the study protocol, the principles of GCP and the appropriate reporting requirements.

Signature ……. Date…….....
Print Name …… Site Name/I.D. …….

7. RESPONSIBILITIES

Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust

	Responsibility to:	Responsible Party	If responsibility is delegated, name body / individual that it is delegated to:
1. Study preparation	a) Ensure that insurance or indemnity arrangements are in place to cover liabilities.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	b) Secure and administer funding for the Study.	Sponsor	Chief Investigator
	c) Secure and contract for the supply of resources including medicinal products/devices/CRO services.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	d) Ensure that the appropriate contracts and agreements are in place for the Study.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
2. Applications and Registration	a) Ensure that the Protocol has undergone independent scientific and statistical review and is compliant with the relevant regulations/ guidelines.	Sponsor	
	b) Prepare Participant information sheet and consent form and other relevant documents to the Sponsor prior to ethics submission.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit/Dr Brian Buckley
	c) Prepare and submit ethics application.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	d) Register the Study with an appropriate protocol registration scheme.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	e) Obtain NHS permission.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit/PI at site

	Responsibility to:	Responsible Party	If responsibility is delegated, name body / individual that it is delegated to:
3. Protocol Amendments	a) Prepare and submit proposed substantial amendments of the Protocol to the, relevant ethics committee and NHS Site.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	b) Ensure all investigators are aware of dates of approval and implementation of all such amendments.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
4. Study Conduct	a) Ensure that legislation in relation to research is followed within the Site	Sponsor	PI at site
	b) Ensure that the Study Site team members are appropriately qualified and experienced to undertake the conduct of the Study and that they have current substantive or honorary employment contracts in place, where required.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit.
	c) Ensure that no Participant is recruited until a favourable ethical opinion has been provided	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	d) Ensure that no Participant is recruited to the Study until satisfied that all relevant permissions and approvals have been obtained.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	e) Put and keep in place arrangements to allow all investigators to conduct the Study in accordance with the Protocol and Clause 2 of this Agreement	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	f) Ensure that the Study is managed, monitored and reported as agreed in the Protocol.	Sponsor	Chief Investigator / Newcastle Clinical Trials

	Responsibility to:	Responsible Party	If responsibility is delegated, name body / individual that it is delegated to:
	g) Ensure that the rights of individual Participants are protected and that they receive appropriate medical care whilst participating in the Study.	Sponsor	PI at site
	h) Maintain and archive Study documentation at the Site.	Sponsor	PI at site
	i) Ensure that all data and documentation are available for the purposes of monitoring, inspection or audit and that the appropriate consent has been provided by the Participant.	Sponsor	PI at site
	j) Inform appropriate health or social care professionals if their patient is a Participant in the Study in accordance with the Research Governance Framework.	Chief Investigator	PI at site
	k) Ensure adequate facilities, resources and support are available to conduct the Study at the Site.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit & PI at site
	l) Report suspected research misconduct.	Sponsor	Chief Investigator
	m) Notify the relevant ethics committee of the end of the Study.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	n) Notify the relevant ethics committee if the Study is terminated early.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
5. Adverse events	a) Maintain detailed records of all adverse events as specified in the Protocol.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	b) Report adverse events as agreed in the Protocol and to legal requirements and in accordance with Trust policy.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	c) Promptly inform ethics committees and investigators of any urgent safety measures taken to protect Participants in the Study.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit

	Responsibility to:	Responsible Party	If responsibility is delegated, name body / individual that it is delegated to:
	d) Ensure that annual safety reports and end of Study reports are generated and submitted to the relevant ethics committee within the required timeframes.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	e) Ensure that all investigators are, at all times, in possession of the current relevant safety information for the Study.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
6. Data Management	a) Design of case report forms and database.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	b) Ensure appropriate analysis of data.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit/Trial statistician
7. Publication	a) Initiate and coordinate review and submission of abstracts, posters and publications.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
8. Archiving	a) Ensure that all Study records are archived appropriately on conclusion of the Study and retained for a minimum of five (5) years	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
9. Clinical Trials	a) Ensure that the Study is conducted in accordance with the principles of Good Clinical Practice (GCP).	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	b) Ensure that all Serious Adverse Events (SAE), other than those specified in the Protocol as not requiring immediate reporting, are promptly assessed as regards the requirement for expedited reporting to the relevant ethics committee.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit
	c) Ensure that SAEs are reviewed by an appropriate committee for the monitoring of trial safety.	Sponsor	Chief Investigator / Newcastle Clinical Trials Unit

8. PROTOCOL SUMMARY

Full Title: INVESTIGATE - I (INVasive Evaluation before Surgical Treatment for Incontinence Gives Added Therapeutic Effect?): a pragmatic multicentre pilot study to assess the feasibility of a future randomised controlled trial

Short title: INVESTIGATE - I a pragmatic multicentre pilot study to assess the feasibility of a future randomised controlled trial

Protocol version: 1.1

Protocol date: 01/07/2011

Chief Investigator: Paul Hilton

Study registration: Current Controlled Trials ISRCTN71327395
http://www.controlled-trials.com/ISRCTN71327395

Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust

Funder: NETSCC Health Technology Assessment Programme (project no. 09/22/136)

Study design: A mixed methods pragmatic multicentre pilot study to assess the feasibility of a future randomised controlled trial. There are four components: (1) a pragmatic multicentre randomised pilot trial (external or rehearsal pilot) to assess patient recruitment and willingness to be randomised, rehearse methodology, and provide outcomes data to inform sample size calculations for a subsequent definitive trial; (2) a national survey of clinicians' views about their willingness to enter their patients in a definitive trial; (3) qualitative interviews with a subset of women to explore their reasons for agreeing (or not) to participate, and their experiences of the pilot trial; (4) qualitative interviews with a small subset of clinicians to explore how they use the results of invasive urodynamic tests to inform their decisions, and to illuminate the questionnaire responses.

Study interventions: **1. Multicentre pilot trial**

Within the multicentre pilot trial, patients will be randomised to one of the following 'intervention' arms:

Arm 1: basic clinical assessment supplemented by ***non-invasive*** tests as directed by the clinician; these may include frequency/volume charting or bladder diary, mid-stream urine culture, urine flow rate and residual urine volume measurement (ultrasound).

Arm 2: basic clinical and non-invasive tests as above, plus ***invasive*** urodynamic testing. Usually this will be dual channel subtracted cystometry with simultaneous pressure/flow voiding studies. Given the pragmatic nature of

the trial videourodynamics and long-term ambulatory bladder pressure monitoring may also be included at the discretion of the clinician.

2. National survey of clinicians:

An online (‘*SurveyMonkey.com*’) or paper questionnaire covering respondents’ views about, access to, and current use of IUT, their willingness to randomise patients within a definitive trial and (for those unwilling to randomise) their reasons for this view.

3. Qualitative patient and clinician interviews

Semi-structured interviews using prompt guides developed from a literature review and discussions within the project team.

Study objectives: To inform the decision of whether to proceed to the definitive randomised controlled trial INVESTIGATE-II, and whether any refinements to the design or conduct of that trial are warranted.

Study outcome: The confirmation or otherwise that units are able to identify the required number of eligible women and recruit them. The acceptability of the investigation strategies (as manifested through recruitment and retention levels), the feasibility and acceptability of the data collection tools (completion rates and quality of data) and clinical data to determine the sample size for the INVESTIGATE-II trial.

Study sites: Tertiary Urogynaecology, Female Urology, and General Gynaecology units in Newcastle, Leicester, Swansea, Sheffield, Northumberland, Gateshead.

Study population: Recruits to the pilot trial will be women with a clinical diagnosis of stress urinary incontinence (SUI) or stress predominant mixed urinary incontinence (MUI), whose family is complete, and who have undergone a course of pelvic floor muscle training (PFMT) (+/- other nonsurgical treatments for their urge symptoms) with inadequate resolution of their symptoms, where both the woman and clinician agree that surgery would be an appropriate and acceptable next line of treatment.

Members of the British Society of Urogynaecology (BSUG) and British Association of Urological Surgeons Section of Female, Neurological and Urodynamic Urology (BAUS-SFNUU) will be invited to take part in the clinician survey.

A purposively sampled subset of women eligible for the trial (including some who agree and some who did not agree to participate) will be included in the patient qualitative interview study.

A small subset of clinicians responding to the paper or web-based survey will be included in the clinician qualitative interview study.

Study duration: Total duration 24 months, with recruitment to the pilot trial anticipated over nine months and follow-up six months after intervention.

9. INTRODUCTION

9.1. BACKGROUND

Urinary incontinence (UI), whilst rarely life-threatening, may seriously influence the physical, psychological and social wellbeing of affected individuals. The impact on the families and carers may be profound, and the resource implications for the health service considerable. Prevalence figures for UI range from 5% to 69% in women 15 years and older, with most studies in the range 25–45%; more severe UI is reported in 4-7% of women under 65 years, and around five million women over 20 years of age in England and Wales may be affected,(1) of whom 65-85% have stress (SUI) or mixed incontinence (MUI).(2) A recent UK study estimated the annual cost to the NHS of treating clinically significant UI in women at £233m, with total annual service costs (including costs borne by individuals) of £411m.(3)

Several methods are used in the assessment of UI to guide management decisions, and invasive urodynamic tests (IUT) may form part of this. Essentially these investigations evaluate functional aspects of the lower urinary tract; cystometry, the most commonly used invasive test, looks at the pressure/volume relationships during bladder filling and emptying, with a view to defining a functional as distinct from symptomatic diagnosis. The costing report associated with the NICE clinical guideline on UI used an estimated charge of £176 for each IUT, and calculated the annual national cost of urodynamic investigations as over £22m.(4) From this, the potential saving from not undertaking urodynamic investigations before conservative treatment was estimated at approximately £3m.(4)

Changes in available operative techniques are leading to dramatic alterations in surgical practice, and Hospital Episode Statistics (HES) demonstrate a 48% increase in surgery for SUI over the last 5 years, with 13,322 procedures in England 2007-08.(5) The NICE costing report estimated further cost savings of £321,000 from more rational use of investigations before surgery, although this is perhaps a conservative estimate, being based on current use of 70% (actual figure probably closer to 100%) and future use of 50%.(4) A more realistic estimate of annual savings based on 2007-08 national tariff costs (£425) and HES activity data would be approximately £3.4m.

Urodynamic tests comprise a group of investigations used to evaluate function of the lower urinary tract; some of these are invasive (requiring catheterisation) and some non-invasive. The tests are most often used for diagnosis and prediction of treatment outcome, although they are also used serially to monitor the progress of disease or as outcome measures in clinical research. Whilst cystometry is the most commonly used IUT, videocystometry and long term ambulatory bladder pressure monitoring are used by some. The current position of IUT in the diagnostic pathway is not agreed, and practices vary considerably; in a UK survey in 2002 only half of the units surveyed had guidelines on indications for the tests, and 85% carried out cystometry in all women with incontinence.(6) Current guidance from NICE suggests that cystometry is not required prior to conservative treatments, and that there is no evidence to support its use prior to surgery where the diagnosis of SUI is likely.(7)

NICE, HTA, Cochrane and the International Consultations on Incontinence (ICI) have all recently undertaken systematic reviews on the subject of urodynamics, and all emphasise the lack of high quality primary research confirming clinical utility.(7-10) The specific aim of the current study is to assess the feasibility of a future large RCT to address a key research recommendation of the NICE

and Cochrane reviews of the subject. It was also among the top prioritised uncertainties identified within the recent James Lind Alliance research priorities setting exercise.[11, 12]

A decision analysis study from the USA failed to find support for invasive urodynamics before surgery in women likely to have SUI.(13) A similar economic assessment within the NICE report on UI, using assumptions more applicable to current NHS practice found that for every 10,000 patients assessed there would be approximately 13 additional cures using invasive urodynamics, at an additional cost per cure of £26,125. With 'a willingness to pay' threshold of £20,000 per quality-adjusted life year (QALY) each cure would have to generate 1.3 QALYs for invasive urodynamics to be considered cost effective;(7) a recent UK randomised trial found that surgery for SUI generated only 0.8 QALYs per procedure, suggesting that preoperative IUT would not be cost-effective.(14)

One small RCT showed no significant benefit from cystometry prior to conservative treatment, although this had methodological issues confounding interpretation.(15) In a cohort study from the North Thames region, women were no more likely to benefit from incontinence surgery if they had undergone preoperative urodynamic testing,(16) and a US study of Medicare patients found that those who had preoperative testing appeared more likely to develop urge incontinence after their surgery.(17) A secondary analysis of data from a US randomised surgical trial found that preoperative investigation did not predict failure or postoperative voiding dysfunction.(18)

9.2. RATIONALE FOR AN INITIAL FEASIBILITY PILOT STUDY

Although NICE, HTA, Cochrane and the ICI have all called for large high quality primary research to establish the clinical utility of invasive urodynamic investigations, there are several reasons to conduct a pilot trial and feasibility assessment before undertaking a definitive trial.

- The sample size for a definitive trial was considered using estimates and assumptions from the modelling exercises cited above,(7, 13) and from a previous surgical trial.[14, 19] However, such calculations are very sensitive to parameter values such as the proportion of recruits with SUI,[13] the proportions of poor outcomes in the two arms, and the effect size of interest. The currently available information is insufficient to plan a study. Given the possible size of a definitive trial on this question, a feasibility study is crucial to test assumptions made, give relevant estimates of key parameters, and inform power calculations for the definitive trial.
- IUT has been widely used in clinical practice over the last 30 years, and despite the lack of evidence of clinical utility, many clinicians look on cystometry as a mandatory part of the investigation of patients with UI, particularly prior to surgical treatment.(20-22) A recent unpublished survey has shown a high level of disagreement with the NICE guidance in this respect,(23) and others have questioned the safety of the recommendations.(24) Hence we need to establish whether sufficient clinicians are in equipoise, and willing to enrol and randomise patients within a definitive trial.
- Patients may not so easily see the importance of 'testing a test' in the same way as they might view testing a treatment. Indeed they are willing and often keen to undergo investigation (even when this is invasive), in the belief that this will inevitably guide them and their clinicians towards appropriate treatment, and away from inappropriate and possibly harmful interventions. Two recent HTA-funded trials of radiography for low back pain were only able to recruit 23% and 51% of patients who were approached to enter the randomised arms.(25, 26) Hence, it is necessary to investigate patients' willingness to take part in an RCT of this particular diagnostic test and to identify barriers to and facilitators of participation.

9.3. OTHER ON-GOING STUDIES

During the development of this protocol the investigators became aware of two other trials currently on-going, looking at the clinical utility of urodynamics in similar patient groups. One is from the Urinary Incontinence Treatment Network in the USA (Value of Urodynamic Evaluation – ValUE - http://www.controlled-trials.com/mrct/trial/472073/urodynamic),(27) and the other from a multicentre group in Netherlands (Value of Urodynamics prior to Stress Incontinence Surgery - VUSIS-2 - http://www.controlled-trials.com/mrct/trial/474127/vierhout).(28) In the VUSIS study all women undergo invasive urodynamic testing; only those women with discordant clinical and urodynamic findings are randomised between surgical treatment (as dictated by their clinical assessment) and individual treatment (dictated by the combination of clinical and urodynamic results). This therefore addresses a rather different clinical question. In the ValUE study women with a clinical diagnosis of SUI or stress predominant MUI are randomised to either no further assessment or to undergo urodynamic investigation (as in INVESTIGATE-I).

Both these are definitive trials using a non-inferiority design; VUSIS does not define a non-inferiority margin; ValUE defines a margin of 11%, which we consider somewhat high *i.e.* we would look on a difference in outcome between groups of 11% as being clinically quite significant, and a difference that might potentially influence the decisions of both clinicians and patients.

We are aware that an earlier study from the Netherlands group (VUSIS-1 - http://www.controlled-trials.com/mrct/trial/385179/urodynamic) was terminated prematurely for unspecified reasons. We are also aware that although ValUE has now completed recruitment, the investigators encountered problems with lack of clinician equipoise (Norton, personal communication).

The primary outcome of both these studies is based on the Urogenital Distress Inventory (UDI) score at 12 months (ValUE using a somewhat arbitrary 70% reduction in UDI along with a PGI-I of '*very much better*' or '*much better*' as indicating treatment success). Although we prefer the use of international standard outcomes as intended by the International Consultation on Incontinence modular Questionnaires (ICIQ) as our primary outcome, we have now chosen to include the UDI as an additional secondary outcome.(29) If we subsequently proceed to the definitive trial INVESTIGATE-II, assuming the other studies do complete recruitment and publish their results, this will allow easier comparison of results, and inclusion in meta-analysis.

Overall therefore, while we are encouraged to see that others look on this topic as being an important clinical uncertainty, we remain of the opinion that a feasibility study is an important step before embarking on a definitive trial using public funds.

10. STUDY OBJECTIVES

Our main objective is to determine the feasibility of undertaking a definitive randomised trial of invasive urodynamic testing (IUT), compared to basic clinical assessment and non-invasive tests, in women potentially suitable for surgical treatment of stress (SUI) or stress predominant mixed urinary incontinence (MUI).

10.1. SPECIFIC OBJECTIVES

10.1.1. To carry out a pilot study (external or rehearsal pilot),(30) randomising patients between basic assessment and IUT.

Outcome measures will include: rates of patient recruitment and retention, willingness to be randomised, and logistics of the definitive trial methodology.

10.1.2. To survey relevant clinicians to assess their likely extent of 'buy-in' to a future definitive trial. This will include their views on cystometry in this particular context and their willingness to randomise patients within a definitive trial.

Invitations to complete an online 'Survey Monkey' questionnaire will be sent out via the research committees of the British Society of Urogynaecology (BSUG) and the British Association of Urological Surgeons Section of Female, Neurological and Urodynamic Urology (BAUS-SFNUU) in order to encourage responses. We will include brief details of the intended definitive study as part of the survey material (*vide infra*).

10.1.3. To carry out qualitative interviews with a purposively sampled subset of women approached to participate in the pilot trial, to explore their reasons for participation or non-participation, and their experiences of the pilot trial procedures. Their responses may help not only in the evaluation of feasibility of a definitive trial, but also in the planning and optimising of recruitment and retention in such a trial.

10.1.4. To undertake a further small series of qualitative interviews with surgeons to explore their decision-making in detail, and the role of IUT within it, and begin to identify potential obstacles to their not using IUT in some patients included in a future definitive randomised trial.

10.2. THE DEFINITIVE TRIAL

If feasibility is demonstrated, we envisage proceeding to a definitive trial (INVESTIGATE-II) to address the question of whether IUT affects the treatment decisions in SUI and the clinical and cost effectiveness of the treatment. That is to say, whether carrying out IUT gives added value over basic clinical assessment with non-invasive tests, not in diagnostic terms but in allowing the most appropriate course of treatment to be identified. Outcomes for the definitive trial will include the post-treatment urinary leakage (quantified), the impact on general health and condition-specific quality of life, adverse effects from investigation or treatment, the health economic outcome in terms of the costs of care with and without invasive tests, and the quality-adjusted life years gained. Thus, in the definitive trial, we hope to establish whether IUT should indeed be offered to all women prior to surgery. The logistics of this definitive trial, including the methods of collecting data on the proposed clinical, patient-reported and economic outcomes, will be rehearsed in full in the pilot study.

11. STUDY DESIGN

This is a mixed methods pragmatic multicentre pilot study to assess the feasibility of a future randomised controlled trial. There are four components:

1. a pragmatic multicentre randomised pilot (external or rehearsal pilot) trial to assess patient recruitment and willingness to be randomised, rehearse methodology, and provide outcome data to inform sample size calculations for a subsequent definitive trial
2. a national survey of clinicians' views about their willingness to enter their patients in a definitive trial
3. qualitative interviews with a subset of women to assess their reasons for agreeing (or not) to participate, and their experiences of the pilot trial
4. qualitative interviews with a small subset of surgeons to assess how they use the results of invasive urodynamic tests inform their decisions, and to illuminate the questionnaire responses.

11.1. PRAGMATIC MULTICENTRE RANDOMISED PILOT TRIAL

11.1.1. UNITS RECRUITING TO THE TRIAL

Should a definitive trial prove to be feasible, recruitment is anticipated to be open to any UK centre offering IUT prior to surgery for SUI or MUI (to be invited via the NIHR Reproductive Health & Childbirth and Urology Clinical Specialty Groups, and via the BSUG and BAUS-SFNUU). However, recruitment to the pilot trial will be limited to six specified units; these are a mix of specialist urogynaecology (Newcastle and Leicester) and female urology (Sheffield and Swansea) departments in university teaching hospitals, providing secondary and tertiary level care, and general gynaecology units in district general hospitals, providing secondary care services (Wansbeck Hospital in Northumberland, and Gateshead). The clinical leads (see section 1.2) in the first four mentioned units are all grant-holding co-investigators on the study; the clinical leads in the latter two units are associated with the CI through the Northern Deanery Urogynaecology Interest Group, and though the Northumberland, Tyne and Wear CLRN Local Specialty Groups (for Reproductive Health and Childbirth).

11.1.2. INCLUSION AND EXCLUSION CRITERIA

11.1.2.1. INCLUSION CRITERIA

Inclusion criteria for the pilot trial (and currently anticipated inclusion criteria for the future INVESTIGATE-II trial) are as follows; women must fulfil ALL criteria to be eligible:

- Women with a clinical diagnosis of SUI or stress predominant MUI
- Women must state that their family is complete
- Women should have undergone a course of pelvic floor muscle training (+/- other non-surgical treatments for their urge symptoms) with inadequate resolution of their symptoms
- Both the woman herself and her treating clinician should agree that surgery is an appropriate and acceptable next line of treatment.

11.1.2.2. EXCLUSION CRITERIA

For the pilot trial (and, as currently anticipated, for the future INVESTIGATE-II trial) the following situations exclude eligibility:

- Symptomatic utero-vaginal prolapse requiring treatment
- Previous surgery for urinary incontinence or pelvic organ prolapse
- Urodynamic investigation within the last three years
- Neurological disease causing urinary incontinence
- Current involvement in competing research studies, e.g. studies of investigation or treatment of urinary incontinence
- Unable to give competent informed consent

11.1.3. WITHDRAWAL OPTIONS

There are two withdrawal options:

1. Withdrawing completely (i.e. withdrawal from the allocated investigation protocol and provision of follow-up data)
2. Withdrawing partially (i.e. withdrawal from the allocated investigation protocol [including a request to move to the alternative investigation arm] but continuing to provide follow-up data by attending clinic and completing questionnaires).

The latter is the preferred option of the research team, but women will be at liberty to withdraw completely.

Consent will be sought from participants choosing option 1 to retain data collected up to the point of withdrawal and to complete an 'end of study' visit at the time of withdrawal. Participants' reasons for withdrawal will be recorded; this information will be used to refine the protocol for the main study.

11.1.4. RECRUITMENT

Potential trial recruits will be identified by the study research nurses prior to attending new or follow-up appointments for SUI or MUI in the clinics run by the unit clinical leads. The Patient Information Sheet (PIS) (see separate document) will be sent out with new appointments or with a reminder letter to attend follow-up appointments; this will allow any questions that the woman may have about the study to be addressed at the one visit. Those declining to take part would undergo further investigation and or treatment as appropriate at the same visit. Those agreeing to take part will sign a study consent form (see appendix 1).

If other potential recruits become apparent only at the time of a clinic visit, they will be invited to take part in the study, and will be given verbal and written information. After a period of at least 24 hours to read, consider and discuss the information with family and/or friends, the research nurse will contact the patient by telephone to respond to any further outstanding questions, and review their decision regarding involvement.

11.1.5. RANDOMISATION

Randomisation will be undertaken by an internet-accessed computer randomisation system held by the Newcastle Clinical Trials Unit (NCTU); randomisation will be stratified by centre. Further investigation will be undertaken where appropriate at the same visit or a later one, as per local custom, and the treatment plan formulated.

Patients within the pilot study will be randomised to receive either:

- basic clinical assessment supplemented by ***non-invasive tests*** as directed by the clinician; these may include frequency/volume charting or bladder diary, mid-stream urine culture, urine flow rate and residual urine volume measurement.

  or

- basic clinical and non-invasive tests as above, plus ***invasive urodynamic testing*** (IUT). Dual-channel subtracted cystometry with simultaneous pressure/flow voiding studies is the most commonly applied technique in the evaluation of patients prior to surgery for SUI in most centres; videourodynamics and long-term ambulatory bladder pressure monitoring are used as alternative or additional invasive tests in some units; given the pragmatic nature of the trial, these tests may also be included at the discretion of the clinician.

11.1.6. BASELINE ASSESSMENT OF STUDY OUTCOMES

Following consent and randomisation, patients will be given a pack of baseline study outcome questionnaires (see paragraph 12.), along with a prepaid envelope. They will be asked to complete the questionnaires at home, and post their responses to the Trial Manager at the NCTU.

11.1.7. SUBSEQUENT TREATMENT WITHIN THE TRIAL

Following investigation, women randomised to the control arm of the study, *i.e.* those treated on the basis of clinical assessment and non-invasive tests, will undergo surgical treatment (see flow chart below). Given the pragmatic nature of the study, the choice of operation will be left to the individual surgeon and patient; since only primary cases are included, it is anticipated that this will be either a retropubic or transobturator foramen mid-urethral tape procedure in most cases. Those randomised to the 'intervention arm' *i.e.* undergoing IUT will undergo similar surgical treatment if urodynamic stress incontinence (USI) is confirmed. Where other diagnoses are identified they are likely to have alternative treatments offered; these may include bladder retraining, antimuscarinic drug treatments, neuromodulation, botulinum toxin injections (where detrusor overactivity [DO] is diagnosed), or clean intermittent self-catheterisation (where a voiding dysfunction is identified). Exactly which of these interventions are chosen will depend on what conservative treatments have been used before entry into the trial; *e.g.* if a woman has tried pelvic floor muscle training plus bladder retraining before entry, she is likely to be offered antimuscarinic drug treatment if detrusor overactivity is shown on IUT. In all centres the treatment algorithm employed will be in keeping with current NICE recommendations.(7) In some cases where mixed abnormalities are reported, women may first undergo one or more of these interventions (to stabilise bladder overactivity, or improve voiding efficiency) and then proceed to surgery for SUI.

11.1.8. FOLLOW-UP

Clinicians will arrange post-operative follow-up or other out-patient review, as per their normal practice and timing.

Patients will be sent a pack of follow up study outcome questionnaires along with a prepaid envelope by the NCTU at six months after the start of treatment. This will be six months following surgery (in IUT and control arms), or six months after the start of non-surgical interventions (in control arm). This will apply in all cases, even where surgery is planned as a secondary intervention in those women initially treated non-surgically. They will be asked to complete the questionnaires at home, and return them to the NCTU. Those failing to return questionnaires within one month of the initial request will be contacted by the appropriate research nurse by telephone, to encourage responses.

11.2. NATIONAL SURVEY OF SURGEONS' VIEWS

11.2.1. SURVEY PARTICIPANTS

Contact details of all members will be obtained from the BSUG and BAUS-SFNUU.

11.2.2. QUESTIONNAIRE DETAILS AND VALIDATION

The survey questionnaire will contain both open and closed questions and will ask for the respondents' views about, access to, and current use of IUT. We will also include brief details (a 'vignette') of the design of the proposed definitive trial as part of the survey material, and seek to ascertain their willingness to participate and to randomise patients within such a trial; for those unwilling to randomise we will seek to establish their reasons for this view. The questionnaire will be piloted (using cognitive interviewing methods) on a group of clinicians who are not BSUG or BAUS-SFNUU members, to assess comprehensibility and content validity and will be refined as needed prior to 'going live'.

11.2.3. QUESTIONNAIRE PROCESSING

An invitation to complete either an online ('SurveyMonkey.com') or paper questionnaire will be sent to BSUG and BAUS-SFNUU members from the offices of the chairs of their respective research committees. Those circulated will be encouraged to use the online version of the survey to facilitate rapid data entry and analysis; we would provide an option to contact the NCTU for a paper version with freepost envelopes for those preferring postal returns. Two reminders, at three and six weeks after initial contact, will be used to stimulate response, and the data set of responses will be closed and prepared for analysis twelve weeks after initial contact; experience in previous surveys shows that the majority of responses is obtained within this period. The survey results will be disseminated, by presentation at a national multidisciplinary meeting, at the earliest opportunity, and before proceeding to a definitive trial.

11.3. QUALITATIVE INTERVIEWS WITH WOMEN

Interviews will be carried out to explore women's understanding and their experiences of the study, the consent processes and their decision to participate. A sub-sample of participants will be invited to take part in this interview study. Purposive sampling will be used to include women from a range of ages, trial participation status (did not agree to randomisation; randomised and retained to final follow-up; randomised but did not provide full follow-up data), allocation status (IUT or basic assessment), treatment received (surgery or conservative management), and study site.

The PIS will include a description of this part of the study, and an indication that women might be approached for interview; it will be made clear that participation in the randomised trial itself does not commit them to taking part in interviews.

If selected, women who do not agree to being randomised within the trial would be approached as soon as possible thereafter for interview. Women who do agree to randomisation will be approached at the end of the trial itself, so as to capture both their reasons for agreeing to participe, and also their overall experience of taking part in the study.

The interviews will be carried out by an expert qualitative interviewer and, with permission of interviewees, all interviews will be audio-recorded and transcribed verbatim. The interviews will be semi-structured using a prompt guide with broad topic areas but the emphasis will be on encouraging women to discuss their own perspectives freely. The prompt guide will be developed from a literature review and discussions within the project team and will be modified as the interviews progress to incorporate issues raised by earlier interviewees. The purpose of the interviews will be to explore women's understanding and experience of the study, their decisions around participation and their perceived barriers to and facilitators of participation in an RCT. This information will inform the decision of whether to proceed to a definitive RCT (i.e. whether women are likely to participate) and will enable us to refine the content of the information given to women and the recruitment and data collection procedures used.

Data collection and analysis will be iterative. Data analysis will be carried out by Dr Natalie Armstrong and an experienced research associate, using the constant comparative method and NUD*IST software. Data collection will continue until theoretical saturation has been reached, i.e. the point at which interviews no longer generate new concepts. It is anticipated that 25-30 interviews will be required. Transcripts will be read three to four times and open codes will initially be applied line-by-line to the data to represent the meaning or significance of each sentence or group of sentences. Generation of the open codes will proceed sequentially, with no attempt at this stage to impose any framework on the data. The open codes will then be incrementally grouped into organising categories or themes. These categories will be modified and checked constantly as further open codes are incorporated as analysis proceeds. When categories have been created to express all of the open codes, explicit specifications will be written for each of the categories to assist in determining under what circumstances data should be assigned to any given category. The categories and their specifications (the coding scheme) will then be programmed into the QSR NUD*IST qualitative software. The coding scheme will be used to process the dataset systematically by assigning each section of text to a category, according to the category specifications.

11.4. QUALITATIVE INTERVIEWS WITH SURGEONS

To better understand surgeons' interpretation of IUT, and how they use the results to decide on the most appropriate treatment option, we will undertake a series of telephone interviews with a purposive sub-sample of surgeons who participate in the initial web/postal survey. The survey form will include a description of this part of the study along with a 'tick-box' option to agree to their being approached for interview, and to provide appropriate contact details.

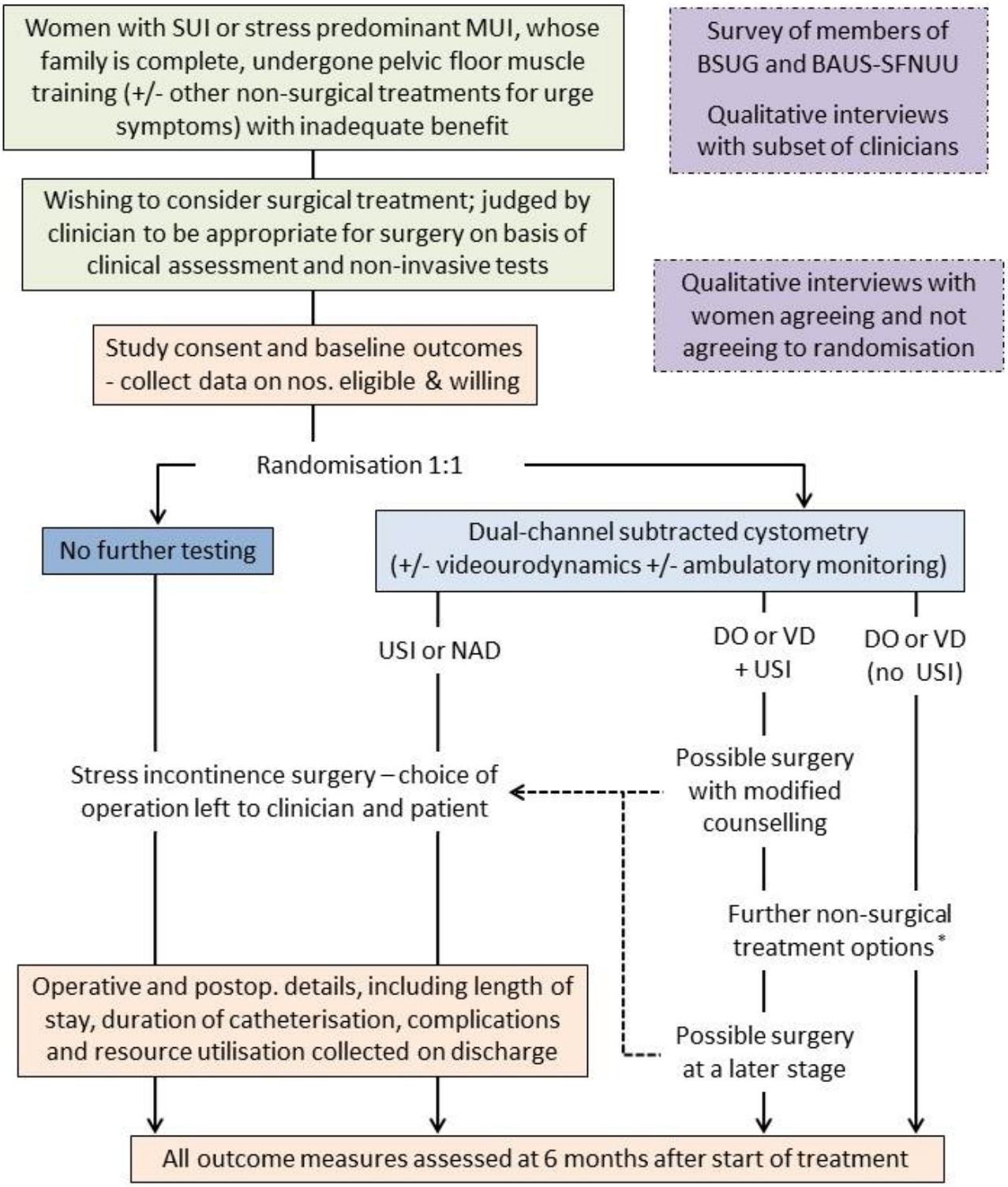
The interviews will enable us to explore surgeons' decision-making in detail, and the role of IUT within that decision-making process, and begin to identify potential obstacles to their not using IUT in some patients included in a future definitive randomised trial. Twelve interviews should ensure that a range of views are represented, *e.g.* both those who do and do not currently use IUT, those who feel it is an important part of their decision-making and those who do not, those who indicate they would be willing to take part in a later trial and those who would not. Interviews will

be short in duration (approximately 15 minutes); analysis will identify key themes related to the use of IUT and possible involvement in a later trial.

Figure 1: Flow diagram of pilot rehearsal trial

A flow diagram is given overleaf, illustrating the study design and the flow of participants.

INVESTIGATE-I Trial



* The choice of non-surgical treatments is left to the clinician and patient, but may include bladder retraining, drugs, neuromodulation, botulinum toxin injections, and clean intermittent catheterisation, depending on IUT results, local protocols and previous trials of therapy.

USI= urodynamic stress incontinence; DO= detrusor overactivity; VD= voiding dysfunction; NAD= no abnormality detected

12. STUDY OUTCOME MEASURES

12.1. RATES OF RECRUITMENT, RETENTION AND RESPONSE

From the pilot trial we are primarily concerned to determine the number of eligible patients in each unit, and the rates of patient recruitment, randomisation, retention and response.

12.2. OUTCOMES IN THE FUTURE DEFINITIVE TRIAL (INVESTIGATE-II)

We intend to use patient reported outcome measures (PROM) as opposed to the more traditional methods for the quantification of leakage as the primary outcome for the future definitive trial INVESTIGATE-II. The currently favoured primary outcome is:

- The combined symptom score of the International Consultation on Incontinence female lower urinary tract symptoms questionnaire (ICIQ-FLUTS) at six months after treatment.(19)

Secondary outcomes will include:

- General health questionnaire (SF-12),
- Quantification of urinary leakage (three day bladder diary, and ICIQ-UI SF)
- Prevalence of symptomatic 'de novo' functional abnormalities including voiding dysfunction and detrusor overactivity (using subscales in ICIQ-FLUTS, with cystometric investigation in symptomatic patients)
- The impact of urinary symptoms on quality of life (ICIQ-LUTSqol and UDI).
- EQ-5D
- Utility values from the EQ-5D and from SF-12 data collected using the algorithm provided by the SF-6D (see section 17 for further details of the economic analysis).

12.3. DATA COMPLETION RATES

We will pilot the collection of the above outcome measures in the feasibility study, to assess data yield (*e.g.* percentage of recruited participants returning completed questionnaires) and quality (*e.g.* completeness and consistency of responses within returned questionnaires). This information will be used to guide the choice and mode of administration of questionnaires and data collection tools in the later definitive trial INVESTIGATE-II.

13. END OF STUDY

For the purposes of reporting to REC, the end of the pilot rehearsal trial (INVESTIGATE-I) will be defined as the time of the last recruited patient's six-month follow-up visit.

14. ADVERSE EVENTS

14.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – refers to an event in which 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
- **Requires re-admission to hospital-, or prolongation of existing inpatient's hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

14.2. EXPECTED ADVERSE EVENTS FROM INVESTIGATION OR TREATMENT

Whilst it is anticipated that incidents of SAEs stemming from the investigation protocols within the INVESTIGATE-I trial would be rare, there are a number of common and well documented consequences of the surgical and medical treatments that patients may subsequently undergo within the trial. These should be reported in exactly the same way as those resulting directly from trial interventions.

A list of the common and well documented consequences of IUT and treatments anticipated to take place within the trial, less common side effects and rare events can be found in Appendix 2.

By definition, a number of women in this trial will proceed to elective surgery for the management of their SUI/MUI, and this will require hospitalisation. Hospitalisation for this indication will NOT be reported as a SAE.

14.3. REPORTING PROCEDURES

All AEs and SAEs should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning AE reporting should be directed to the CI in the first instance.

14.3.1. NON SERIOUS ADVERSE EVENTS

All such events, whether expected or not, should be recorded.

14.3.2. SERIOUS ADVERSE EVENTS

All SAEs shall be reported to the Newcastle Clinical Trial's Unit within 24 hours of the PI learning of the occurrence. A secure fax line is available for this purpose (Fax no.: +44 (0) 191 222 8901)

The initial report should contain the following minimum information*:

1. Study identifier (Protocol number)
2. Participant's unique study number
3. Participant's date of birth
4. Event description
5. Start date of event
6. Reason for severity grading (i.e. death, life-threat, hospitalisation, disability/incapacity or other)
7. Reporters name, signature and date

*In the case of incomplete information at the time of the initial reporting, all appropriate information should be provided as follow-up as soon as it becomes available.

Hospitalisations for elective treatment of a pre-existing condition (whether SUI/MUI or otherwise) do **not** need reporting as SAEs. Unrelated hospitalisations will be elicited at the follow up appointment, scheduled subsequent appointments and all emergency appointments.

All SAEs should be reported to the REC where in the opinion of the CI, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs should be submitted within 15 days of the CI becoming aware of the event, using the NRES SAE form for non-IMP studies.

Local investigators should report any SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Contact details for reporting SAEs
Fax: 0191 222 8901, attention NCTU INVESTIGATE-I Trial Manager

15. STATISTICAL AND QUALITATIVE ANALYSES

The primary outcome for the main trial is the ICIQ-FLUTS combined symptom score. There are relatively little data on the parameters of this measure in a relevant patient population. Sample size for pilot trials is typically determined pragmatically, with recommendations of a minimum of 30 participants per arm. We aim to obtain 60 responses per trial arm, and allowing for 50% losses at recruitment, randomisation and response stages (see justification in detailed description), estimate that a total of 240 eligible patients should be approached.

The statistical analyses of the pilot trial and clinician survey will be descriptive in nature, providing estimates of key trial parameters for the definitive trial, to inform power calculations and other aspects of trial design for INVESTIGATE-II. The pilot trial data will be analysed after all patients have completed six month follow-up.

Data collection from qualitative interviews will continue until theoretical saturation has been reached, i.e. until interviewing is no longer generating new concepts. It is anticipated that the analyses of the interviews and survey will proceed during the recruitment and follow-up phases of the pilot study. Data analysis will be carried out by Dr Natalie Armstrong and an experienced Research Associate using the constant comparative method, assisted by NUD*IST software. Transcripts will be read three to four times and open codes will initially be applied line-by-line to the data to represent the meaning or significance of each sentence or group of sentences. Generation of the open codes will proceed sequentially, with no attempt at this stage to impose any framework on the data. The open codes will then be grouped incrementally into organising categories or themes. These categories will be modified and checked constantly as further open codes are incorporated as analysis proceeds. When categories have been created to express all of the open codes, explicit specifications will be written for each of the categories to assist in determining under what circumstances data should be assigned to any given category. The categories and their specifications (the coding scheme) will be programmed into the QSR NUD*IST qualitative software. The coding scheme will be used to process the dataset systematically by assigning each section of text to a category, according to the category specifications.

16. DATA COLLECTION AND RETENTION

To preserve confidentiality, all patients and clinicians will be allocated a unique study identifier, which will be used on all data collection forms and questionnaires; names and addresses will not appear on completed questionnaires or case report forms. Only a limited number of members of the research team will be able to link this identifier to patient- or clinician- identifiable details (name and address) which will be held on a password-protected database. All study documentation will be held in secure offices, and the research team will operate to a signed code of confidentiality. Transmission of identifiable data between study sites, NCTU and the Newcastle upon Tyne Hospitals NHS Foundation Trust (the study Sponsor) will be by secure fax, registered post or carried by a study team member. A clinical data management software package (Symphony) will be used for data entry and processing, allowing a full audit trail of any alterations made to the data post entry. Original questionnaires, case report forms and consent forms will be securely archived at the Newcastle upon Tyne Hospitals NHS Foundation Trust archive facility for five years following publication of the last paper or report from the study.

17. ECONOMIC ANALYSIS

The pilot study will rehearse the data collection for the economic evaluation which includes health state utilities and costs to the NHS and patients. To inform the definitive economic analysis, the pilot study will assess consistency of resource use in administration of the IUT and other tests, surgical and non-surgical treatments, the ease of access to information from hospital databases about resource use. It will also pilot the use of data collection instruments.

17.1. COLLECTION OF DATA

17.1.1. OUTCOME DATA

A cost-utility analysis will be performed in the definitive trial, and the pilot study will rehearse the collection of health state utilities for each participant. These data will be obtained using self-administrated SF-12 and EQ-5D questionnaires. The questionnaires will be completed by participants at baseline and at six months follow-up.

17.1.2. COST DATA

To obtain data on the type and grade of staff present in the consulting room and operating theatre, we will approach each participating centre to determine the staff mix in each centre with respect to the procedure. The costs of tests and treatments will be obtained from each participating centre or constructed based on the resource used to provide each specific procedure. Costs will be based on data from the following sources: the cost per unit of time for each grade of staff involved based upon the Unit Cost of Health and Social Care.(31) The consumables and reusable item cost will be derived from manufacturers' price lists.

17.1.2.1. COSTS OF IUT TEST AND OTHER TESTS

Health service usage of the IUT test will be recorded in the Case Report Form (CRF) for every participant in the intervention arm. Within the pilot study we will assess the completeness of data recorded on the CRF. The specific information to be recorded for economic analysis includes:

1) Time of patient entry into and leaving the consulting room
2) Grade and type of operator present
3) Grade of other staff present
4) Post-investigation complications

There are a number of non-invasive tests that may also be performed for patients in both intervention arm and control arm, and these are:

- Frequency/volume charting or bladder diary
- Mid-stream urine culture
- Urine flow rate
- Residual urine volume measurement (ultrasound)

17.1.2.2. COSTS OF SURGERY AND OTHER TREATMENTS

Within the trial the main costs will be those associated with surgery (including staff, consumables, capital and overheads). The following information on the use of surgery will be recorded in the CRF for every participant in the study:

1) Grade of anesthetist present at operation
2) Type of anaesthesia (general, regional, local +/- sedation)
3) Time of patient entry into and leaving operating room
4) Time of patient entry into and leaving recovery room (if applicable)
5) Grade of surgeon present
6) Grade of other staff present
7) Date of admission
8) Date of discharge (if date of discharge is the same as admission it will be assumed that the procedure was performed as a day case)
9) Postoperative complications

Other treatments will be offered to patients in the intervention arm who are not diagnosed with SUI or MUI. These treatments include:

- Bladder retraining
- Antimuscarinic drug treatments
- Neuromodulation
- Botulinum toxin injections (where detrusor overactivity [DO] is diagnosed)
- Clean intermittent self-catheterisation (where a voiding dysfunction is identified)

17.1.2.3. USE OF NHS HEALTH SERVICES

Participant Costs Questionnaire (Part A and Part B) will collect data on the use of NHS health services and patients' out-of-pocket expenses. Use of NHS services will be collected retrospectively using Part A of this questionnaire. Use of secondary care services will include non-trial protocol outpatient visits and readmissions relating to urinary incontinence. Use of primary care services will include prescription medications, contacts with primary care practitioners e.g. GPs, practice etc and contact with continence nurses or physiotherapists.

17.1.2.4. PARTICIPANTS OUT-OF-POCKET EXPENSES

At six months follow-up, participants will provide information about their use of non-NHS health services and related out-of-pocket expenses through the Participant Costs Questionnaire (Part A and Part B). Part B of the questionnaire will collect information on participants travel and time costs with regard to their access to the NHS health services. Within the pilot we will investigate the impact on response rates of administering Part B of the Participant Costs Questionnaire administered at the six month follow-up compared with collecting data at two to four weeks after the standard six month follow-up. This will provide information as to whether this questionnaire will reduce the response rate of participants.

Participant costs will comprise four elements: self purchased healthcare and related products; time and physical costs of activities due to urinary incontinence related condition, for example, doing extra laundry; travel costs for accessing NHS care; and time costs of travelling and attending NHS care;

Estimation of self purchased health care and other management costs (From Part A of the Participant Costs Questionnaire)

Self-purchased health care will include over the counter medications and purchase of containment products, such as incontinence pads. Private health insurance cost will be included if the insurance is purchased for urinary incontinence related conditions. Management costs of urinary

incontinence related conditions, such as the costs of doing extra laundry, will also be included. This will include time cost of doing the extra laundry and money spent for using a laundrette if applicable.

Estimation of travel and time costs for accessing care (From Part B of the Participant Costs Questionnaire)

Estimation of travel costs requires information on the number of visits to each location of care e.g. a GP. The participants will be asked in part B of the Participant Costs Questionnaire, for each type of visit, which mode of transport they used and how much the fare was for one way if they travelled by bus, taxi or train, or how many miles they travelled and how much they paid for parking if they used private car. Estimation of participants' time costs will be collected in a similar manner. The questionnaire will ask how long they spent travelling to and attending each type of health care provider. Participants will also be asked what activity they would have been undertaking (e.g. paid work, leisure, housework) had they not attended the health care provider. These data will be presented in their natural units, e.g. hours and minutes, and attached monetary value using standard economic conventions, e.g. the Department of Transport estimates for the value of leisure time.(32) These unit time costs, measured in terms of their natural and monetary terms will then be combined with estimates of number of health care contacts to calculate patients' time costs. If someone has accompanied them, the same questions will be asked for the accompanying person.

17.2. COST UTILITY ANALYSIS

In the full trial, a cost-utility analysis is planned, based on utility scores derived from SF-12 and EQ-5D scores at baseline and at the end of 6 months follow-up. The primary analysis will the incremental cost per QALY at six months, where QALYs are based upon the responses to the EQ-5D converted into QALYs using the area under the curve method.(33) The results will be presented as point estimates of mean incremental costs, QALYs, and incremental cost per QALY. Cost-utility analysis will also be conducted where QALYs are based upon SF-6D scores derived from responses to the SF-12.(34) In the pilot study, we will rehearse the cost-utility analysis, which may inform the study hypothesis for the definitive trial as well as informing the analysis plan for the definitive trial.

18. REGULATORY ISSUES

18.1. ETHICS APPROVAL

The conduct of this study will be in accordance with the ethical principles set out in the Declaration of Helsinki (2008) and in accordance with the Research Governance Framework for Health and Social Care (2nd edition, 2005).(35)

Application for ethical approval will be made to a REC appropriate to multi-domain research through the Integrated Research Application System (IRAS). Application for R&D approval will be made via the NIHR Co-ordinated System for gaining NHS Permissions (NIHR CSP). Local R&D approval of the protocol will be sought prior to recruitment commencing at each site.

18.2. CONSENT

Women will be informed about the detail of the study, including possible benefits and risks of participation by means of a patient information leaflet (designed with input from service users), and by discussion with the local research nurse responsible for recruitment. This will be done independently of the clinician responsible for on-going care, and of staff undertaking investigations. All patients in the study will provide written informed consent before any study procedures are carried out. Separate written informed consent to take part in the qualitative patient interview sub-study will be sought, and it will be made clear to trial participants that they are under no obligation to take part in the qualitative sub-study. Written informed consent to take part in the clinician interviews will be sought. Return of a completed questionnaire will be taken as indicative of implied consent to participate in the clinician survey.

Patients will be informed that they have the right to withdraw from the study at any time, without giving reasons if they do not wish to and without prejudicing their further investigation or treatment. Although, to inform the design of the INVESTIGATE-II trial, we will ask those who do not agree to participate in the trial or who withdraw prematurely for their reasons for withdrawal, the right to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to recommend alternative investigation or treatment to that specified in the protocol at any stage if the clinician feels it is in the participant's best interest, but the reasons for doing so will be recorded. In these cases the participant remains in the study for the purposes of follow-up and data analysis.

18.3. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and the Sponsor organisation will ensure that the study is registered under the Data Protection Act 1998.

18.4. INDEMNITY

Indemnity in respect of negligent conduct will be covered by the individual PIs' and researchers' employing NHS Trusts and / or personal professional indemnity arrangements. Indemnity in respect of protocol authorship will be provided through Newcastle University's public liability

insurance. Indemnity in respect of study management will be provided by the Newcastle upon Tyne Hospitals NHS Foundation Trust, in its role as sponsor. There is no provision for indemnity in respect of non-negligent harm.

18.5. SPONSOR

Newcastle upon Tyne Hospitals NHS Foundation Trust will act as the sponsor for this study. Delegated responsibilities will be assigned to the Newcastle Clinical Trials Unit (NCTU).

18.6. FUNDING

The study is funded by the NETSCC Health Technology Assessment programme (HTA ref 09/22/136).

18.7. AUDITS

The study may be subject to inspection and audit by the Newcastle upon Tyne Hospitals NHS Trust under its remit as sponsor and by other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition) 2005.(35)

18.8. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the NCTU.

18.8.1. TRIAL MANAGEMENT GROUP

Day to day running of the trial will be overseen by a Trial Management Group (TMG), comprising, at a minimum, the Chief Investigator (PH), together with the NCTU-based Trial Management Team (TMT, comprising Senior Trial Manager, Trial Manager, Assistant Trial Manager), the trial statistician, data manager and project secretary; other members of the research team will participate, either face-to-face or via teleconference, on an 'as needed' basis. TMG meetings will take place on a regular basis throughout the duration of the study; the frequency of these meetings will be greater in the early months of the study (when sites are being set up etc.) and towards the end (when data are being analysed). Email and the web-based BASECAMP application will be used for correspondence and document sharing between meetings, both within the TMG and between the TMG and other members of the research team. The TMG will have responsibility for ensuring the compliance and progress of the study in relation to all regulatory (ethics, R&D), administrative (finance and adherence to contract, reporting to funders), academic (e.g. data accrual and management; maintaining project time lines; generating trial reports; considering protocol amendments) and clinical/safety issues (e.g. dealing promptly with the concerns of study sites, Serious Adverse Event collation and reporting to relevant authorities). The Trial Master File (TMF) will be compiled and held by the TMT at the NCTU.

18.8.2. TRIAL STEERING COMMITTEE (TSC)

The TSC (membership listed above) will provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder (HTA) and will ensure that the trial is conducted in accordance with

the principles of Good Clinical Practice (GCP). The Terms of Reference for the TSC are set out in Appendix 4. The TSC will concentrate on progress of the trial against projected rates of recruitment and retention, and against the schedule set out below, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question. The safety and well-being of the trial participants are the most important considerations and will prevail over the interests of science and society. The TSC will provide advice, through its independent Chair, to the Chief Investigator, the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial. Representatives of the Trial Sponsor and the Trial Funder will be invited to all TSC meetings, and minutes of all TSC meetings will be provided to the Trial Sponsor and Trial Funder.

18.8.3. DATA MONITORING AND ETHICS COMMITTEE (DMEC)

The focus of the DMEC will be on safety and ethical issues; its terms of reference are set out in Appendix 5 and a formal charter will be agreed and adopted at its first meeting. The DMEC will make recommendations to the TSC, Sponsor, Funder and research team on whether there are any ethical or safety reasons why the trial should not continue (given that this is a pilot trial of established technologies we think it unlikely that premature stopping will be recommended). The DMEC will initially meet face to face in Newcastle to determine its terms of reference and modes of operating etc., but thereafter may hold subsequent meetings by teleconference/web conference.

The DAMOCLES charter will be used as the basis for the DMEC's terms of reference.(36) DMEC membership will comprise an independent chair, an independent statistician and one other member, independent of the research team, with relevant content area and/or methodological expertise.

18.8.4. ON-SITE MONITORING

The chief investigator and trial manager will make a 'start-up' visit to each of the participating sites at the initiation of the trial. They will ensure that all those involved in the trial are knowledgeable in the protocol and procedures, and may contribute to other local staff awareness of the trial. They will ensure that trial documentation is available, and that mechanisms are in place for secure data storage. Pre-visit site initiation checks on essential documents will be made. The trial manager will make periodic monitoring visits to each of the participating sites for the purpose of monitoring of study documentation and subject consent including version control, source data verification (SDV) (on a risk-based basis; we do not anticipate 100% SDV), maintenance of ICHGCP consent training for all staff, and other related study documentation tasks etc. Central monitoring, including review of completed case report forms (CRFs), resolution of data queries, and identification of data outliers, using statistical methods, will also be carried out by the trial management team, data manager and statistician.

19. PUBLICATION POLICY

The results of the study will be published as a monograph for the NETSCC HTA; the CI (Paul Hilton) will be first author, and each of the grant holding co-investigators will be co-authors unless they cease to maintain contributions to the work and/or do not approve the final draft of publications approved by other co-authors.

The study may be presented at scientific conferences and other similar events, and may be published as research papers in academic and popular clinical journals.

In order that the trial results and other research outputs are disseminated as widely and accessibly as possible, reports will also be prepared for lay readership as well as for health care provider audiences. These will be published where possible and appropriate through the general media and through the publications and websites of relevant patient and carer organisations. The Bladder and Bowel Foundation will provide support in this regard.

Authorship on peer-reviewed publications arising from this rehearsal pilot trial will include the CI, and grant holding co-investigators and members of the trial management team as appropriate; all authors must fulfil ICMJE criteria for authorship.(37) Co-investigators and collaborators not fulfilling authorship criteria for any particular publication will be acknowledged.

The NETSCC HTA will be acknowledged on each publication. Draft publications will be submitted to HTA for approval at least 28 days prior to submission.

No individual patient participating in the trial will be identifiable from any study report.

20. PROJECT TIMETABLE AND MILESTONES

Quarter	Start date	End/by date	Activity
Pre-study	01/09/2010	30/12/2010	Agree trial documentation: formal protocol, patient information; consent forms; questionnaires; survey materials, CRF; apply for ethics and R&D approval.
Year 1, Q1	04/01/2011		Official trial start date
	04/01/2011	04/04/2011	Set up administrative base; trial staff assigned or appointed
		31/01/2011	Set up meeting with HTA
	01/02/2011	15/03/2011	Initiation visits to 6 clinical sites
		31/03/2011	1st (joint) DMEC & TSC meeting
		31/03/2011	All clinical staff to confirm current GCP training
Year 1, Q2	01/04/2011	27/12/2011	Patient recruitment proceeding on all sites
		30/04/2011	1st collaborators meeting
	01/04/2011	28/09/2011	Qualitative interviews with women (declining to participate)
Year 1, Q3	01/07/2011	23/09/2011	Survey of clinicans, including reminders x2
		01/07/2011	1st progress report to HTA
		29/08/2011	Expected recruitment 50% (120 women approached)
		31/08/2011	2nd collaborators meeting
		30/09/2011	2nd DMEC meeting
Year 1, Q4	01/10/2011	27/06/2012	Patient 6 month follow-up questionnaires will be posted out from trial office.
	01/10/2011	30/11/2011	Analysis of survey results
		31/10/2011	2nd TSC meeting
	01/10/2011	27/06/2012	Qualitative interviews with women (agreeing to participate)
	01/11/2011	28/07/2012	Tracing of non-responders to follow-up questionnaires; contact by local research nurses.
	01/11/2011	30/01/2012	Preparation of abstract for presentation and manuscript for publication of survey results
		27/12/2011	Expected recruitment complete (240 women approached)
		01/01/2012	2nd progress report to HTA
Year 2, Q1 & 2	01/01/2012	29/06/2012	Qualitative interviews with surgeons
		31/01/2012	3rd DMEC meeting
		28/02/2012	3rd TSC meeting
Year 2, Q3	01/07/2012	29/09/2012	Analysis of qualitative study results
		01/07/2012	3rd progress report to HTA
		31/07/2012	All follow-up data collected
		31/08/2012	Database locked for analysis
	01/09/2012	31/10/2012	Analysis of main study results.
		30/09/2012	3rd collaborators meeting
Year 2, Q4	01/10/2012	30/12/2012	Preparation of abstracts for presentation and manuscripts for publication of main study results. Depending on study outcome, formulation of outline bid to HTA for definitive trial
	01/10/2012	30/12/2012	Preparation of abstract for presentation and manuscript for publication re: interviews
		14/01/2013	Final study report to HTA