INVESTIGATE-I (INVasive Evaluation before Surgical Treatment of Incontinence Gives Added Therapeutic Effect?): a mixed-methods study to assess the feasibility of a future randomised controlled trial of invasive urodynamic testing prior to surgery for stress urinary incontinence in women

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Scientific summary

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Scientific summary

Background

Urinary incontinence (UI), while rarely life-threatening, may seriously influence the physical, psychological and social well-being of affected individuals; the impact on the families and carers may be profound, and the resource implications for health services considerable. Prevalence figures range from 5% to 69%, and around 5 million women over 20 years of age in England and Wales may be affected.

Urodynamic tests comprise a group of investigations used to evaluate lower urinary tract function; some of these are invasive (i.e. require catheterisation) [invasive urodynamic test (IUT)] and some non-invasive. The tests are most often used for diagnosis, planning of appropriate intervention and prediction of treatment outcome. The current position of invasive urodynamic testing in the diagnostic pathway for UI is not agreed and practices vary considerably: in a UK survey in 2002, 85% of units carried out invasive urodynamic testing in all women with incontinence. Current guidance from the National Institute for Health and Care Excellence suggests that invasive urodynamic testing is not required prior to conservative treatments for UI, nor prior to surgery where the diagnosis of stress UI (SUI) is clear on clinical grounds [i.e. where there are no symptoms of overactive bladder (OAB) or voiding difficulty, no anterior compartment prolapse, and no previous surgery for SUI].

The National Institute for Health and Care Excellence, National Institute for Health Research (NIHR) Health Technology Assessment, The Cochrane Collaboration and the International Consultation on Incontinence (ICI) have each undertaken systematic reviews on the subject of urodynamics and called for further high-quality primary research confirming clinical utility.

Objectives

The objective of INVasive Evaluation before Surgical Treatment of Incontinence Gives Added Therapeutic Effect? (INVESTIGATE-I) was to inform the decision of whether or not to proceed to a definitive randomised controlled trial (RCT) of invasive urodynamic testing, compared with basic clinical assessment and non-invasive tests, in women potentially suitable for surgical treatment for SUI or stress predominant mixed UI (MUI); in addition we sought to determine whether or not any refinements to the design or conduct of that future definitive trial were warranted.

Design

This was a mixed-methods feasibility study with five components:

1. A pragmatic multicentre randomised pilot trial 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. An exploratory economic evaluation undertaken within the pilot RCT.
3. A national survey of clinicians' views about their use of invasive urodynamic testing and willingness to enter their patients in a definitive trial. In light of emergent literature, an update to the survey was undertaken 2 years after the initial survey in 2013.
4. Qualitative interviews with a subset of clinicians responding to the initial survey to explore whether or not and how they use the results of invasive urodynamic testing to inform their decisions and to illuminate the questionnaire responses.

5. Qualitative interviews with a subset of women eligible for the trial to explore their reasons for agreeing (or not) to participate and their experiences of the pilot trial.

Setting

The initially planned pilot trial sites were urogynaecology and female urology units in Newcastle upon Tyne, Leicester, Swansea and Sheffield, and gynaecology units in Northumberland and Gateshead. An additional site at South Tees and Patient Identification Centres in Sunderland and South Tyneside, were subsequently included.

Participants

Recruits to the pilot trial were women with a clinical diagnosis of SUI or stress predominant MUI, whose family was complete and who had undergone a course of pelvic floor muscle training (± other, – surgical treatments for their urge symptoms) without improvement, and where the patient and clinician agreed that surgery was an appropriate and acceptable next treatment.

Members of the British Society of Urogynaecology and British Association of Urological Surgeons Section of Female, Neurological and Urodynamic Urology were invited to take part in the web-based clinician survey. A subset of respondents was invited to take part in the interview study.

A subset of women eligible for the trial was invited to take part in the patient qualitative interview study.

Interventions

Within the multicentre pilot trial, patients were randomised to either:

- **control** (the no IUT arm): basic clinical assessment supplemented by non-invasive tests as directed by the clinician; these included frequency/volume charting or bladder diary, mid-stream urine culture, urine flow rate and residual urine volume measurement (by ultrasound), or
- **intervention** (the IUT arm): basic clinical and non-invasive tests as above, plus invasive urodynamic testing. Usually this was dual-channel subtracted cystometry; given the pragmatic nature of the trial, videourodynamics and ambulatory urodynamics were permitted at the clinician's discretion.

The clinician survey was an online questionnaire hosted on the www.surveymonkey.com server covering respondents' views about access to, and use of, invasive urodynamic testing, their willingness to randomise patients within a definitive trial and (for those unwilling to randomise) their reasons for this view.

The qualitative patient and clinician interviews comprised semistructured interviews using prompt guides developed from a literature review and discussions within the project team.

Trial outcome measures

The main outcome of the INVESTIGATE-I study was the confirmation or otherwise that units are able to identify the required number of eligible women and recruit them. Additional outcomes were 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 the acquisition of clinical data from which to determine the sample size for a future definitive trial.

All proposed outcome measures for that future definitive trial were piloted in INVESTIGATE-I. The primary outcome for the proposed definitive trial was the combined symptom score of the ICI Modular Questionnaire (ICIQ) Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) at 6 months after treatment.

Secondary outcomes included: general health questionnaires Short Form 12 (SF-12) and EuroQol-5D (EQ-5D); quantification of urinary leakage [3-day bladder diary and ICIQ Urinary Incontinence Short Form (ICIQ-UI SF)]; prevalence of symptomatic 'de novo' functional abnormalities including OAB and VD (using subscales in ICIQ-FLUTS); the impact of urinary symptoms on quality of life [ICIQ Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol) and Urogenital Distress Inventory (UDI)]; utility values from the EQ-5D-3 Level and from Short Form 6D derived from responses to the SF-12; use of NHS services; NHS and patient costs; and quality-adjusted life-years derived from the utility values.

Results

Randomised pilot trial

All the proposed trial processes likely to be required in a future definitive RCT of invasive urodynamic testing versus clinical assessment and non-invasive testing were effectively rehearsed within the pilot study. Overall, 771 women were screened for the pilot trial and 37% of women screened were eligible for inclusion. There was wide variation between centres in the number of women identified as eligible (14–399) and in the conversion rate from screening to recruitment (19%–57%), despite trial staff following a screening protocol. Overall, 78% of eligible women identified were recruited (total = 222); there were considerable delays in recruitment with variation in accrual rates between sites and delays in regulatory requirements contributing to the failure to meet the target of 240 participants.

Baseline questionnaires were completed by 75% of participants, although only 56% (63% of those circulated) returned the follow-up questionnaires at 6 months after start of treatment. Although the rate of return of questionnaires was lower than expected, missing data within the returned booklets were few. The ICIQ-FLUTS overall score could be calculated for 98% of subjects at baseline; ICIQ-UI SF, ICIQ-LUTSqol and overall UDI score could be calculated for 99%, 95% and 84%, respectively. At 6 months' follow-up the ICIQ-FLUTS overall score could be calculated for 90% and the ICIQ-UI SF, ICIQ-LUTSqol, and overall UDI score for 91%, 87% and 81%, respectively. A small number of participants returned blank follow-up questionnaires, although most of these included some annotation to indicate that the respondent was free from symptoms. Bladder diaries were less often completed than questionnaire booklets; only 68% of the baseline diaries and 53% of the 6-month follow-up diaries were returned. All scales demonstrated a reduction in mean score in response to treatment at the 6-month follow-up, although the distribution of scores at follow-up was more positively skewed, suggesting that while most women had experienced considerable relief of their presenting symptoms, some had not. A small number of women elected to defer treatment, although 95% of women in the control arm underwent surgical treatment, compared with 80% in the IUT arm, reflecting changes in the management plan following invasive urodynamic testing.

Economic evaluation

The economic evaluation rehearsed data collection and analysis to inform a future definitive trial. A two-part patient-costs questionnaire was returned by 56% (part A, use of services and out-of-pocket expenses) and 54% (part B, time and travel costs of accessing services); of those returned, the majority were completed appropriately. Part of the low response rate was caused by the closure of the database for analysis before data collection was complete.

Survey of clinicians

The response rate for the initial survey was 34% (176/517); all respondents had access to invasive urodynamic testing and 89% currently arranged investigation for most women with SUI or stress predominant MUI. For a variety of scenarios with increasingly complex symptoms, few clinicians were in equipoise as to whether or not invasive urodynamic testing was appropriate. Nevertheless, 70% rated the

research question underlying the INVESTIGATE studies as 'very important' or 'extremely important' and 68% recorded a 'willingness to randomise' score ≥ 7/10.

Given the length of time between the circulation of the initial survey (August 2011) and the publication of this report, a further brief update to the survey was undertaken (June 2013). There were 145/498 (29%) responses; 68% still rated our research question as 'very important' or 'extremely important' and 61% recorded a 'willingness to randomise' score ≥ 7/10. That is, there was no obvious shift in surgeons' opinions on the subject despite other recently published studies. One hundred and four out of 145 (72%) respondents provided an e-mail address indicating their interest to participate in a future definitive trial.

Qualitative clinician interviews

Eighteen clinicians responding to the original survey were interviewed. The majority of those using invasive urodynamic testing routinely were convinced of its clinical utility in helping to decide treatment and counsel patients, although a small number reported that their practice, in relation to invasive urodynamic testing, was influenced more by local norms than any personal commitment to it on their part. In contrast, those who used invasive urodynamic testing relatively rarely saw little additional benefit from its use but recognised significant potential costs (e.g. in terms of time, financial implications and infection risk). While some clinicians' views on the importance of a future definitive trial were shaped by genuine uncertainty about the value of invasive urodynamic testing, more commonly the research question was regarded as important because clinicians believed they personally knew the answer and wanted research in order to change others' practice and bring it in line with their own. This could lead to clinicians not in equipoise being unwilling to randomise their patients. There were examples of clinicians who regarded invasive urodynamic testing as essential and were unwilling to have some of their patients denied it, but also of those who currently did not use invasive urodynamic testing who would be willing enter their patients into either arm.

Qualitative patient interviews

Although all were invited, no eligible patients who declined randomisation in the pilot trial agreed to interview. A diverse sample of 111 trial participants was invited for interview; 36 agreed, of whom 29 were interviewed. Women's first reactions to receiving the invitation to participate in the trial were almost exclusively positive. Women's reasons for participation were often altruistic and included wanting to help research and to help others with the same condition, and no particular participation burden was perceived. The specific nature of the study and the intervention being assessed was an important factor for some women who were concerned about the possibility of having invasive tests performed; some subsequently randomised to the 'no further testing' arm reported being very pleased with this allocation; others randomised to the intervention arm subsequently withdrew.

Reactions to the written study information were mostly positive – it was regarded as clear and informative and there was enough information for women to be able to make a decision about taking part. Participants' understanding of the study was broadly good, although there were some cases in which people appeared confused about the overall aim. The principle of random allocation to one of two possible groups was generally well understood.

The baseline questionnaires were generally described as simple to fill in, easy to understand and straightforward. While some actually viewed completing the 6-month follow-up questionnaires positively (as it underlined how successful the treatment had been), others reported finding them burdensome and irrelevant now they had few or no symptoms to report.

Discussion

The pilot trial identified several important issues for the planning of a future definitive trial. It appeared that greater clarity in the definition of terms used within the inclusion and exclusion criteria for eligibility might assist trial staff to identify potential recruits. In addition, given that information relevant to recruitment was often omitted from general practitioner referral letters, study information could be sent out by default, except when obvious exclusions are specified. Some of the secondary outcomes might be omitted in a future definitive trial, as they provided little extra information; a shorter questionnaire pack might improve response rates in a future definitive trial. Changes to the design of the questionnaire booklets might limit the problem of returning blank questionnaires. If bladder diaries were to be used again, modification to the recording of pad use should be considered.

A cost–utility analysis was rehearsed and procedures for handling data and exploring uncertainties prepared. The results of the economic evaluation are not sufficient to recommend any changes in practice; they do, however, suggest that further research would be of value and several limitations recognised in this evaluation should be addressed in a future definitive trial.

Conclusions

INVESTIGATE-I has achieved its objectives and has shown that a definitive trial is feasible. Despite evidence emerging during the course of these studies, the most recent meta-analysis (published October 2013) and recently surveyed UK clinical opinion (surveyed June 2013) opines that such a large definitive trial is still required.

We have identified several modifications to patient screening, recruitment, retention and staff engagement across multiple sites through the lifetime of a long study, as well as economic evaluation that would be desirable in designing and conducting a future definitive trial. While such a trial would undoubtedly be challenging, requiring between 400–900 recruits across 15–30 sites (depending on the outcome and target difference sought), we have found evidence that a sufficient number of clinicians and patients would take part, such that it could be completed in an acceptable time frame.

Trial registration

This trial is registered as ISRCTN71327395.

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