Author's response to reviews

Title: A mixed methods study to assess the feasibility of a randomized controlled trial of invasive urodynamic testing versus clinical assessment and non-invasive tests prior to surgery for stress urinary incontinence in women: the INVESTIGATE-I study

Authors:

Paul Hilton (paul.hilton@ncl.ac.uk)
Natalie Armstrong (na144@le.ac.uk)
Catherine Brennand (cath.brennand@newcastle.ac.uk)
Denise Howel (denise.howel@newcastle.ac.uk)
Jing Shen (jing.shen@newcastle.ac.uk)
Andrew Bryant (andy.bryant@newcastle.ac.uk)
Douglas G Tincello (dgt4@le.ac.uk)
Malcolm G Lucas (Malcolm.Lucas@wales.nhs.uk)
Brian S Buckley (briansbuckley@gmail.com)
Christopher R Chapple (C.R.Chapple@sheffield.ac.uk)
Tara Homer (Tara.Homer@newcastle.ac.uk)
Luke Vale (luke.vale@newcastle.ac.uk)
Elaine McColl (Elaine.McColl@newcastle.ac.uk)

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Author's response to reviews: see over
Dear Editors

Re: A mixed methods study to assess the feasibility of a randomized controlled trial of invasive urodynamic testing versus clinical assessment and non-invasive tests prior to surgery for stress urinary incontinence in women: the INVESTIGATE-I study.

Thank you for your email of 30/6/2015, regarding our manuscript reference above, submitted on 11/3/2015. My colleagues and I are most grateful to you and the reviewers for the efforts they have gone to in assessing our work, and for their constructive comments. We have been through these in detail, and outline below our responses to the various comments. A revised manuscript has been uploaded through www.trialsjournal.com.

We would be grateful for your further consideration of the revised manuscript for online publication.

Yours sincerely,

Paul Hilton
Retired Consultant Gynaecologist and Urogynaecologist
AUTHORS’ RESPONSE TO EDITOR’S AND REVIEWERS’ COMMENTS

Editorial requests:

1. Please include the email addresses of all authors on the title page.
   
   Added to title page

2. Please include the date of registration with the trial registration number at the end of the Abstract.

   Registered 07/06/2010 – added to abstract

3. Please include the names of all approving Research and Development Offices with your ethics statement in the Methods section.

   Added to methods section

4. For completed randomised controlled trials, Trials requires the submission of a populated CONSORT checklist and flow diagram. If appropriate, please provide the flow diagram and checklist as additional files (http://www.trialsjournal.com/authors/instructions/research#preparing-additional-files). A Word file of the checklist and flow diagram can be downloaded here: http://www.consort-statement.org/consort-statement/.

   We had included the CONSORT flow diagram in our original submission, as figure 1, and retain this here. We have included the checklist as requested as a supplementary file.

Reviewer 1 (document 1854840323172626):

Review

This paper addresses the main results of a feasibility study about the important area of treatments for women with urinary incontinence. A mixed methods approach was used with data collected via multiple methods. The paper reports the results for the multicentre randomized pilot trial and the face-to-face interviews with eligible patients. The authors give a detailed description of the undertaking of the study and the study findings and discuss the limitations and challenges in the conduct of the study. Overall it was a well-presented manuscript with relevant tables and figures to support the results. Table 1 was a very useful way of summarising the findings and evidence.

Thank you

Compulsory Revisions

1. The qualitative adds an important aspect to the understanding of aspects of the conduct of this feasibility study and the results per se are interesting and relevant. The methods refer to continuing interviews until data saturation was reached but this seems
inconsistent with Page 27 which indicates that that all women who were willing were interviewed. Can you please clarify.

Thank you for your comment, but we are not clear why the reviewer takes this view. On page 27 we specifically indicate ‘A total of 36 women indicated they were willing to be interviewed. Of these 29 were interviewed, … and four were not interviewed as they were from groups already well represented in the sample.’ Hence, we do not feel there is any inconsistency in our description.

2. Also can you indicate how was rigor established in the qualitative data analysis phase?

We have added further text to explain that the researcher doing the analysis did so under one of the author’s close supervision, with continual checking and discussion of any differences in interpretation.

3. Participants – you have used quotes from participant 04 and 17 twice- can you please find appropriate quotes from other participants.

We have replaced one quote for each of participants 4 & 17 with alternatives from other participants. We have also replaced one quote for participant 11 with an alternative from another participant, although the reviewer had not spotted we quoted this participant twice.

Minor Revisions

1. Abstract and methods: The paragraph describing aspects of the mixed methods study reads as though there were multiple studies; can you consider describing it as … multicenter randomized pilot trial and; qualitative face-to-face interviews with … etc.

Thank you; the reviewer is correct in interpreting that ‘there were multiple studies’; as we indicate, there were five elements to this mixed methods study. We feel it is important that readers are aware of this mixed methodology, and prefer therefore to retain our description of each of these, whilst indicating that ‘Only the first and second of these elements are reported here.’ We note that the term mixed methods study has become an increasingly well used term within health services research.

2. Define the abbreviations: Page 6 OAB; Page 25 PFMT.

Thank you; these terms are defined in the abbreviations list, but we have added the expansion at first use in the text as requested.

3. Page 11: Given the inconsistency in the term study can you clarify that the ethical approval was for all aspects of the study i.e. randomized pilot and qualitative interviews?

Indeed, all elements of the mixed methods study (including the two elements reported here, highlighted by the reviewer) were covered by the favourable opinion from the Ethics Committee. We have clarified this on page 11.

4. Page 16: For consistency and explanation with the list of outcomes can you give a statement introducing the EQ-5D-3L instrument.
Thank you; for consistency, we have moved reference to the EQ-5D-3L instrument to the generic description ‘general health questionnaires’; we have also added in the copyright details for this instrument.

5. Table 1 needs some minor editing.
Thank you; we have made minor revisions to table 1.

**Discretionary Revisions**

1. Page 21: As the sample numbers are used to indicate the women who screened positive and agreed to randomization could this information be added to table 2.
   Raw numbers have been added into table 2 as requested

2. Can you please consider adding legends for all tables and figures which contain abbreviations.
   We have added an explanation of abbreviations used in tables and figures to the relevant legends. However, abbreviations are also supplied as a separate list, so the editor may choose to use one or other format.

**Reviewer 2 (document 2624882731762983):**

The authors report on a pilot study to assess the feasibility of a randomized controlled trial of invasive urodynamic testing versus clinical assessment and non-invasive tests prior to surgery for stress urinary incontinence (SUI) in women. In this submission the authors report on:

A pragmatic multicenter randomized pilot trial, and
A qualitative face-to-face interview study with patients eligible for the trial.

The authors conclude that between 232 and 922 participants would be needed depending on the target difference in primary outcomes, possible modifications may be needed to the existing protocol and a definitive trial of urodynamics prior to surgery for SUI or stress dominant mixed urinary incontinence is feasible and relevant. The authors should be commended for studying a very important and clinically relevant topic in urogynecology that has been controversial for a long time.

Thank you

**Major compulsory revisions:**

1. There are now two randomized trials from two continents (ValUE and VUSIS) that have demonstrated that preoperative urodynamic studies are not needed for women with uncomplicated predominant SUI. 630 women were included in the ValUE trial which
meets the study population size recommended in this submission so we already know the study is feasible. Although the most recent Cochrane review stated that there is no evidence about urodynamic use in men, children, or people with neurologic disease and large definitive trials are needed in which people are randomly allocated to urodynamics or not, most experts believe the answer has been addressed for preoperative urodynamics in women with uncomplicated SUI before surgery. The question remains whether women with complicated SUI benefit from urodynamics. The authors should address what gap in the literature they would be addressing with this study.

Thank you. We have commented in detail on these two studies on pages 7 & 8 or our manuscript. We would point out however that our study does not look at ‘uncomplicated SUI’ as described by the reviewer, but at women with ‘stress or stress predominant mixed incontinence.’ Clinically, we believe this is an important group for whom the results of the two studies mentioned are not directly relevant – since they represents to some degree the ‘complicated SUI’ referred to.

2. The inclusion criterion does not include the demonstration of stress incontinence (i.e. the sign of SUI, a positive stress test) as part of the clinical assessment and non-invasive testing study arm. This is glaring deficiency and major design flaw. Not including the objective demonstration of SUI can explain some clinician reluctance to participate in this RCT. (I wouldn’t recommend women have SUI surgery without IUT, unless I demonstrated SUI.) Certainly a stress test is non-invasive and could be considered. All the participants in the VaUE trial demonstrated SUI with a positive stress test and the participants in the VUSIS-2 trial demonstrated SUI “on physical exam and/or micturition diary”. In fact, the American College of Obstetrics and Gynecology and the American Urogynecologic Society published, in June 2014 a Committee Opinion, Evaluation of Uncomplicated Stress Urinary Incontinence in Women Before Surgical Treatment, stating: “The minimum evaluation before primary midurethral sling surgery in women with symptoms of SUI includes the following six steps: 1) history, 2) urinalysis, 3) physical examination, 4) demonstration of stress incontinence, 5) assessment of urethral mobility, and 6) measurement of postvoid residual urine volume.” If indeed they perform a “definitive” trial of IUT vs. clinical assessment and IUT is found superior but the clinical assessment does not include the demonstration of stress incontinence, the results will not be definitive and in fact will be uninterpretable and discounted. The authors should address why their clinical assessment does not include these minimal non-invasive measures.

Thank you. We appreciate the reviewer’s views on this point, and acknowledge the ACOG/AUGS statement on ‘Evaluating uncomplicated SUI ...’. We do of course recognise the significance of the demonstration of the clinical finding of stress incontinence in the assessment of women with incontinence; indeed this was part of our initial assessment in these studies, and was collected in our case report forms. We do not however agree that this finding represents an essential inclusion criterion in either feasibility or definitive trials. As indicated above, it was never our intention to look simply at ‘uncomplicated SUI’, but at the larger group of women with ‘stress or stress redominant mixed urinary incontinence, where there remains considerable clinical uncertainty, as shown in one of the other elements of our mixed methods study (a national clinician survey). Many patients presenting with this symptom complex do not have clinically demonstrable stress incontinence. Hence, in addition to extending our inclusions to women with symptoms beyond those of ‘uncomplicated SUI’ we also wished to include those who do not have clinically
demonstrable stress incontinence. We cannot agree that this makes our findings (or those of a future definitive trial) uninterpretable and likely to be discounted; they will simply be generalisable to a more ‘real life’ patient group ultimately (whether IUT is found to be superior or inferior).

3. The authors have chosen ICIQ-FLUTS measure as their primary outcome. As they noted, both groups will have low and significant reductions from baseline. This will be true for almost any measure. The authors should further address why they are using this instrument which is less commonly used than the UDI and does not have accepted MCID measures. Instead “the study team decided that differences of 2, 3, or 4 units would be realistic differences that might be achieved in any comparison of an intervention….” and “it was felt that a difference of around three units would also be of clinical interest”. The authors should explain why they are just deciding on these numbers rather than doing a formal MID assessment of the instrument or consider changing the primary outcome instrument to the UDI.

Thank you. We acknowledge that the UDI has been more widely used in some countries, especially the USA; it was in the knowledge of the ongoing ValUE and VUSIS studies that we chose to include the UDI as a secondary outcome measure. We felt that the International Consultation on Incontinence modular questionnaire was likely to be more widely accepted in the long term. In relation to UDI, as we indicate on page 36, we found this to have a lower completion rate both at baseline and at 6 months follow-up, and hence propose this be omitted from a future definitive trial carried out in UK.

We acknowledge that the lack of MCID did present us with some difficulties; however, we did not have the information to calculate an MCID from the data collected in this pilot trial, and to date no other group has published an MCID for this scale. As we indicate in our discussion, ‘a monograph on ways of specifying a target difference for a trial recommended that estimates of sample size should be determined by more than one approach.’ In any definitive trial, the following data sources might be amongst those considered:

1. Clinician opinion
2. Data from the external pilot trial
3. A value of information study (not included here, but forming part of a separate report)

The research on methods of determining an MCID conducted by a team including world leaders in the field goes on to describe how these different approaches might be optimally used in establishing a MCID. We can confirm that the methods we used are fully compliant with these best practice recommendations.

Minor essential revisions:
none
Minor discretionary revisions:

1. The patient interview study results and patient quotes will not be surprising to readers who perform clinical trials.

   Thank you. Whilst the results of this study might be seen as intuitive, we would respectfully disagree with the reviewer’s rather negative opinion of the value of qualitative research in general, and in patients’ feelings about trial involvement in particular; we see this component of our work as a vital element of the determination of feasibility.

2. Patient incentives will improve response rates.

   We had included this issue in our discussion on page 36.

3. This section can be shortened.

   We have edited the text in this area to ensure it is written more concisely.


