

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of a personalised pelvic floor Muscle Training program on Urinary incontinence after radical Prostatectomy (MaTchUP): Protocol for a randomised controlled trial
AUTHORS	Hodges, Paul; Stafford, Ryan; Coughlin, Geoff; Kasza, Jessica; Ashton-Miller, James; Cameron, Anne; Connelly, Luke; Hall, Leanne

VERSION 1 - REVIEW

REVIEWER	R.F.M. Bevers Leiden University Medical Center Department of Urology Leiden, The Netherlands
REVIEW RETURNED	09-Dec-2018

GENERAL COMMENTS	Interesting study design It duplicates a study published by Dijkstra et al Neurourol Urodyn. 2015 Feb;34(2):144-50
-------------------------	--

REVIEWER	Inge Geraerts KULeuven Department of Rehabilitation Sciences Belgium
REVIEW RETURNED	11-Jan-2019

GENERAL COMMENTS	<p>Dear Author,</p> <p>The topic is very relevant, as urinary incontinence remains a significant problem after radical prostatectomy. Moreover, finding effective methods to reduce this problem is mandatory. The treatment content is relevant for the patients and will certainly decrease their incontinence.</p> <p>However, I have quite some remarks regarding the comparison of both treatment groups and the power calculation in this study protocol.</p> <p>First of all, I am convinced that insisting in patients to not only contract the anal musculature, but also to focus on the urethral muscles (as M.bulbospongiosus, M. puborectalis and M. sphincter urethrae externa) is mandatory. However for me this is conventional training, as this is actually the lift and squeeze principle as it has been taught since several years. Also the</p>
-------------------------	--

inclusion of functional training is an essential part of pelvic floor muscle training.
We also have quite some doubts regarding the power calculation, as the presumed difference of a third to 40% is derived from a study that compared treatment with no treatment and not from two different treatments. For that reason, we doubt that it will be possible to find a significant difference between both groups.
Secondly, in my opinion, it is always necessary to control for pelvic floor muscle contraction via digital examination. When performed well, one can add another kind of feedback and this can be biofeedback, via a probe or transperineal ultrasound or... Whether or not adding a kind of biofeedback will ameliorate the results of the patients, remains unclear in the literature, as many study designs in the past regarding this topic had several methodological limitations.
Thirdly, I want to emphasize that I think it is valuable to offer patients one preoperative session, although several previous studies showed no additional effect of preoperative training. Patients are very grateful for this opportunity and it takes away a lot of issues and questions regarding the content of the postoperative sessions. The authors made a good choice in offering all patients one preoperative session.
Finally, the extensive testing taking into account urinary, bowel, sexual complaints, quality of life, physical activity... is very well chosen.

I am looking forward to your reply.
Kind regards,

Abstract

- This will be compared 'with'...
- Neuromuscular control measures of pelvic floor muscles will be 'performed/done/executed...'

Introduction

- Can you be more precise about how many of the patients still experience urinary incontinence 12 months after surgery, concerning the literature?
- PPI has been identified as the major... , and many live for many years
- Recent physiological research using... □ Sentence is too long. More compact formulating would make the reading more easily.
- ...do not target the aspects of function that need to be trained; and start too late (□ literature?)
- Recent work has highlighted that persistent PPI is associated with...
- Reference n° 9 Cochrane review is updated in 2015
- Supported by this physiological evidence... □ Sentence is too long.
- Your introduction does not mention problems with sexual function and bowel function, as well as physical activity. However, they are an outcome in your study.

Methods

Study design

- Two first sentences are too similar.

Participant recruitment

- Who will screen patients for eligibility and who will recruit them?

- Who will obtain informed consent from participants and when does it occur?
- Consecutive patients (= all patients who had a radical prostatectomy between 27/07/2018 - ...)?

Study Treatments

- All participants will attend ... (□ a synonym would be better here)
- Do the treatments only take place at the Wesley and Princess Alexandra Hospitals or do patients of the treatment groups have to go to physiotherapists in private practices? How many therapists will be involved? (will there be any control for multiple therapists/assessors?)

Data collection

- The primary endpoint at 3 months was selected as... as... (reformulation of the sentence will make the reading more easily)

Treatment adherence

- Use of a synonym of 'to prompt' would be better in one of the last two sentences.

Outcome measures

Secondary outcomes

- Self – assessed 24-hour pad test: a bladder diary will be collected for this period (it would be better to assess the 24-hour pad test multiple days if possible, to control for less physical activity in the patient at that specific day).

Data analysis

Primary endpoint and sample size justification

- Data from seven RCT's indicate ~ 60% of men receiving conventional training still will be incontinent... This overview of the literature offers a rather one-sided overview, as these results are not quite encouraging to start therapy, many other studies found better results indicating continence percentages around 50-80% at 3 months after surgery (Milsom 09, Geraerts 13, Van Kampen 00, Sacco 06, Finley 09, Joseph 06, Patel 07/11; Borin 07...).
- Also the study on which the power calculation was based (Van Kampen et al, Lancet 2000) found continence percentages of 88% 3 months after surgery with conventional training.
- For that reason, supposing a difference of a third to 40% between both experimental groups, is a very optimistic assumption. In the study of Van Kampen et al, this was the difference between training and no training.
- Additionally we wonder how you can exclude that the studies you found in the literature, did not use the technique including the urethral and anal muscles and not only the anal muscles (defined by you as conventional therapy), as I am quite sure that for us and for many other therapists, including the SUS, BS and PR is conventional training
- With these assumptions and sample size... □ Sentence is too long. More compact formulating would make the reading more easily.

Secondary analyses

- Analysis of physical activity (IPAQ) is not mentioned

REVIEWER	Doreen McClurg Glasgow Caledonian University Glasgow G4 0BA
REVIEW RETURNED	14-Jan-2019

GENERAL COMMENTS	My only comments are that the primary OCM of pad weighing is also included as a secondary OCM? Suggest an inclusion criteria that men agree to wear pads - surprising some don't
-------------------------	---

REVIEWER	Sarah R Haile Epidemiology, Biostatistics and Prevention Institute University of Zurich Switzerland
REVIEW RETURNED	31-Jan-2019

GENERAL COMMENTS	<p>This was a very interesting study protocol.</p> <p>I'm wondering if you had considered what limitations the trial might have. Surprisingly, none are listed in the abstract.</p> <p>My main question though is about the power calculation and primary analysis. The study appears to be powered to compare percentage of patients continent at 3 months, a fairly straightforward calculation, even with 3 study arms. In the paragraph "primary analysis" however, a fairly complicated model is described: $\text{continence} \sim \text{time} * \text{treatment} * \text{baseline.control} + \text{surgeon} + \text{random}(\text{physiotherapist})$. Based on the sample size justification, I expected something closer to: $\text{continence} \sim \text{treatment}$, or perhaps: $\text{continence} \sim \text{treatment} * \text{baseline.control}$. Or even: $\text{continence} \sim \text{treatment} * \text{baseline.control} + \text{random}(\text{physiotherapist})$. Nevertheless the sample size justification appears to assume a much simpler model than is described as the primary analysis model. Wouldn't this indicate that more patients are needed? Or that the primary analysis model should be the simpler one corresponding to the sample size calculation, and the model described could be considered as a secondary analysis of the primary endpoint?</p>
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

<p>Reviewer: 1 Reviewer Name: Rob F.M. Bevers</p> <p>Interesting study design It duplicates a study published by Dijkstra et al Neurourol Urodyn. 2015 Feb;34(2):144-50</p>	<p>The study by Dijkstra et al. 2015 differs from the present study in several key aspects. First, the Dijkstra et al. 2015 study involved assessment and feedback of the anal muscles. This is a major point of difference to the present study. Anal muscle contraction provides no information regarding the urethral sphincter muscles. It can only provide information regarding the anal sphincter (which has no role in urethral constriction/urinary continence, and the puborectalis, which has some role in urethral control, but has never been shown to be related to urinary incontinence after prostatectomy). In the present study we will test a major</p>
---	--

	<p>departure from this approach by providing detailed assessment and feedback of all muscles involved in urinary continence, in particular the striated urethral sphincter, which has been extensively shown to be related to continence recovery. This muscle was not assessed in the previous study and not considered as a target for training. Second, the study by Dijkstra states that “All patients from both groups received PFMT with biofeedback and/or electrostimulation if they were still incontinent 6 weeks postoperatively (standard care).” As only 20.8% of men were continent at 6 weeks, this would have applied to most men and would have contaminated the results.</p> <p>Third, the study by Dijkstra et al only involved pre-operative training (plus post-operative self-guided training), which contrasts the pre- and post-operative training provided in this trial. Fourth, the post-operative instructions were to perform 2 sets of 30 contractions per day. This is vastly different from the comprehensive functional training program to be tested in the present study. We have added the following to the text to emphasise some of these differences;</p> <p>“...to compensate for the reduced smooth muscle (which would require capacity for low intensity sustained contraction in addition to strong contraction);”</p> <p>“Digital rectal examination used for assessment and feedback in most previous trials of PFMT for incontinence after prostatectomy¹⁹ provides information of anal sphincter and PR contraction, but cannot provide information of the SUS and BC. Transperineal ultrasound imaging provides a non-invasive and validated²⁰ method to evaluate and provide feedback of PR, SUS and BC, simultaneously.”</p> <p>“...in a manner that matches the individual needs of each man, and trains incorporation of pelvic floor muscle activation into functional tasks (rather than training limited to repeated maximal voluntary contractions),”</p>
<p>Reviewer: 2 Reviewer Name: Inge Geraerts Institution and Country: KULeuven Department of Rehabilitation Sciences Belgium</p> <p>The topic is very relevant, as urinary incontinence remains a significant problem after radical prostatectomy. Moreover, finding effective methods to reduce this problem is mandatory. The</p>	<p>We thank the reviewer for the positive reflection of the significance of the problem we aim to address and the design of our program.</p>

<p>treatment content is relevant for the patients and will certainly decrease their incontinence.</p> <p>However, I have quite some remarks regarding the comparison of both treatment groups and the power calculation in this study protocol.</p>	
<p>First of all, I am convinced that insisting in patients to not only contract the anal musculature, but also to focus on the urethral muscles (as M.bulbospongiosus, M. puborectalis and M. sphincter urethrae externa) is mandatory. However for me this is conventional training, as this is actually the lift and squeeze principle as it has been taught since several years. Also the inclusion of functional training is an essential part of pelvic floor muscle training.</p>	<p>We agree that it plausible to suggest that inclusion of a focus on the urethral muscles should be mandatory in pelvic floor muscle training for incontinence after prostatectomy. This is a key aspect of our new program and the study will inform whether it makes a difference to have this focus. Although the reviewer considers this to be a part of conventional training, it is not common in published randomised controlled trials (RCT). In fact, the largest RCT which contributes substantial weight to the systematic review evidence against pelvic floor muscle training in this patient group does not mention it. We argue that this failure to address the urethral muscles may have contributed to the negative outcome. We have recently completed a systematic review of content of pelvic floor muscle training programs that confirms that consideration of urethral muscles is infrequently included (Hall LM, Aljuraifani R, Hodges PW. Design of programs to train pelvic floor muscles in men with urinary dysfunction: Systematic review. <i>Neurourol Urodyn.</i> 2018;37:2053-87). Further, no studies have used assessment or feedback for the urethral muscles. Thus, it can only be assumed that training of these muscle must be included. Taken together we argue that it is critical to compare the comprehensive approach that includes activation of urethral striated muscles with the approach that only addresses anal contraction to provide a definitive answer. The following has been added to the text for clarification;</p> <p>“Digital rectal examination used for assessment and feedback in most previous trials of PFMT for incontinence after prostatectomy¹⁹ provides information of anal sphincter and PR contraction, but cannot provide information of the SUS and BC. Transperineal ultrasound imaging provides a non-invasive and validated²⁰ method to evaluate and provide feedback of PR, SUS and BC, simultaneously.”</p>
<p>We also have quite some doubts regarding the power calculation, as the presumed difference of a third to 40% is derived from a study that compared treatment with no treatment and not from two different treatments. For that reason, we doubt that it will be possible to find a significant difference between</p>	<p>We are assuming that in the conventional training group 60% of participants will be incontinent at 3 months, and comparing this to the urethral training group, where we are powering to detect a reduction to 40% incontinent.</p> <p>Perhaps some confusion arises because of the way in which this sentence is written: “With 97 men per group, a reduction of incontinence by a third to 40% of men at</p>

<p>both groups.</p>	<p>3 months (conservatively based on the difference identified in a previous study”</p> <p>We have changed this to read: “With 97 men per group, a reduction of incontinence by a third from 60%, to 40% of men at 3 months (conservatively based on the difference identified in a previous study”</p> <p>If there is a true difference between the conventional and urethral training as we have hypothesised, then this sample size does provide 80% power to detect that change with a 5% significance level.</p>
<p>Secondly, in my opinion, it is always necessary to control for pelvic floor muscle contraction via digital examination. When performed well, one can add another kind of feedback and this can be biofeedback, via a probe or transperineal ultrasound or... Whether or not adding a kind of biofeedback will ameliorate the results of the patients, remains unclear in the literature, as many study designs in the past regarding this topic had several methodological limitations.</p>	<p>Although we understand the opinion of the reviewer, it is our contention that transperineal ultrasound imaging provides an unrivalled method to measure and provide feedback of each of the striated muscles that can constrict the urethra, Digital palpation cannot provide information regarding the striated urethral sphincter, which is the muscle considered most critical for urinary continence after prostatectomy. As indicated by the reviewer, it is not clear from the literature whether inclusion of ultrasound imaging will improve outcomes, hence the need for the present study. We have added the following to the text for clarification;</p> <p>“Digital rectal examination used for assessment and feedback in most previous trials of PFMT for incontinence after prostatectomy¹⁹ provides information of anal sphincter and PR contraction, but cannot provide information of the SUS and BC. Transperineal ultrasound imaging provides a non-invasive and validated²⁰ method to evaluate and provide feedback of PR, SUS and BC, simultaneously.”</p>
<p>Thirdly, I want to emphasize that I think it is valuable to offer patients one preoperative session, although several previous studies showed no additional effect of preoperative training. Patients are very grateful for this opportunity and it takes away a lot of issues and questions regarding the content of the postoperative sessions. The authors made a good choice in offering all patients one preoperative session.</p>	<p>We thank the reviewer for the positive comments about inclusion of the pre-operative session.</p>
<p>Finally, the extensive testing taking into account urinary, bowel, sexual complaints, quality of life, physical activity... is very well chosen.</p>	<p>We thank the reviewer for the positive comments about inclusion of these assessments.</p>
<p>Reviewer: 3 Reviewer Name: Doreen McClurg Institution and Country: Glasgow</p>	<p>There is a distinction between the primary and secondary outcomes.</p>

<p>Caledonian University Glasgow G4 0BA</p> <p>My only comments are that the primary OCM of pad weighing is also included as a secondary OCM?</p>	<p>The primary outcome is a dichotomous outcome of continent or incontinent, that is determined based on the pad weight, at 3 months.</p> <p>The secondary outcome is the recorded pad weight in grams.</p> <p>The following text has been moved from the paragraph referring to the primary outcome to the paragraph referring to the secondary outcome measure for clarity. "The measure of pad weight (grams) is recorded as the secondary outcome."</p>
<p>Suggest an inclusion criteria that men agree to wear pads - surprising some don't</p>	<p>Although not a formal inclusion criteria, men are informed of the necessity to do this during the recruitment process both in written form and verbally. Men are only included if they agree with the all aspects of the study.</p>
<p>Reviewer: 4 Reviewer Name: Sarah R Haile Institution and Country: Epidemiology, Biostatistics and Prevention Institute University of Zurich Switzerland</p> <p>This was a very interesting study protocol.</p> <p>I'm wondering if you had considered what limitations the trial might have. Surprisingly, none are listed in the abstract.</p>	<p>We agree that there are limitations that should be mentioned. Limitations have been added to the abstract as follows;</p> <p>"• Possible limitations are adherence to the comprehensive home program and the burden of the extensive follow-up data collection"</p>
<p>My main question though is about the power calculation and primary analysis. The study appears to be powered to compare percentage of patients continent at 3 months, a fairly straightforward calculation, even with 3 study arms. In the paragraph "primary analysis" however, a fairly complicated model is described: continence ~ time*treatment*baseline.control + surgeon + random(physiotherapist). Based on the sample size justification, I expected something closer to: continence3 ~ treatment, or perhaps: continence3 ~ treatment*baseline.control. Or even: continence3 ~ treatment*baseline.control + random(physiotherapist). Nevertheless the sample size justification appears to assume a much simpler model than is described as the primary analysis model. Wouldn't this indicate that more</p>	<p>We agree that the primary analysis should align with the sample size calculation, and that we specified a more complex model in the original version. We have modified the primary analysis section as follows;</p> <p>"Analyses will be by intention-to-treat of all randomised participants. For the binary continence outcome at each time point, a hierarchical logistic regression model including random effects for physiotherapists, terms for treatment group and baseline control and an interaction between them will be fit. The model will also include a term for the stratifying variable of surgeon. For the primary hypothesis, this model will be interrogated to yield differences in the proportions of participants recovering continence at 3 months between the groups and 95% confidence intervals³². The model will be similarly interrogated to determine whether the effect of Urethral training relative to Conventional training is moderated by NM control at baseline. A secondary analysis will fit a longitudinal model for the multiple outcomes from each participant, including random effects for each participant as well as for physiotherapist, and a three-way interaction term</p>

patients are needed? Or that the primary analysis model should be the simpler one corresponding to the sample size calculation, and the model described could be considered as a secondary analysis of the primary endpoint?	between time, randomised treatment group, and baseline NM control, and all 2-way interactions and main effects, as well as a term for surgeon.”
--	---

VERSION 2 – REVIEW

REVIEWER	Sarah R Haile Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland
REVIEW RETURNED	19-Mar-2019

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.
-------------------------	--