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Efficacy of a personalised pelvic floor Muscle Training program on Urinary incontinence after radical Prostatectomy (MaTchUP): Protocol for a randomised controlled trial

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Abstract

Introduction: Prostate cancer is the most common cancer in men. Prostatectomy is the most common treatment. Morbidity from prostatectomy is high - 80% of men experience urinary incontinence which negatively impacts quality-of-life. Post-surgical pelvic floor muscle training is commonly prescribed but recent systematic reviews found no evidence of efficacy. We propose a new treatment that commences pre-operatively and targets functional training of specific pelvic floor muscles that contribute to urinary continence. Assessment and biofeedback using transperineal ultrasound imaging assists training. This will be compared against conventional training (maximal pelvic floor muscle contraction assessed by digital rectal examination), and no training. Embedded physiological studies will allow the investigation of moderation and mediation of the treatment effect on the outcomes.

Methods and analysis: This randomised clinical trial will include 363 men scheduled to undergo radical prostatectomy for prostate cancer. Participants will be randomised into *Urethral training*, *Conventional training*, and *No training* groups. Clinical data will be collected at baseline (1-2 weeks pre-surgery), and post-surgery after catheter removal, weekly to 3 months (primary endpoint), and monthly to 12 months. Outcomes include 24-hour pad weight test (primary), incontinence, quality-of-life and cost effectiveness data. Neuromuscular control measures of pelvic floor muscles will be measured at baseline, post-surgery, 6 weeks, 3 and 12 months. Study assessors and statistician will be blinded to the group allocation.

Ethics and dissemination: This study is registered with the Australian New Zealand Clinical Trials Registry and has ethical approval from university and host hospital Ethics Committees.

Trial outcomes will be shared via national/international conference presentations and peer-reviewed journal publications.

Trial registration number: ACTRN12617000788370 (registered 30th May 2017)

Article Summary

Strengths and limitations of the study

- Uses randomised design in a clearly defined population
- Tests an innovative intervention designed to target mechanisms of urinary continence in men that is based on recent physiological data of mechanisms of continence and incontinence in men
- Uses individualised care based on assessment using new transperineal ultrasound imaging methods to study pelvic floor muscle function
- Includes investigation of mediation and moderation of the treatment effect by pelvic floor muscle neuromuscular control variables

Introduction

Prostate cancer is the most common non-cutaneous cancer in men in Australia and internationally (1 in 7 men) and the second most common cause of cancer death[1]. Radical prostatectomy (prostate removal to prevent metastasis) is a common treatment. The good news is that prostate cancer has very high 5-yr survival - 95%[1]. The bad news is that morbidity is high – almost 80% of men experience incontinence after prostatectomy (post-prostatectomy incontinence: PPI)[2], and many are incontinent beyond 12 months[2]. PPI has been identified as the major determinant of quality of life for these men, and many live for many years with ongoing major cost (up to 33% use incontinence products[3]) and social isolation[4 5]. Introduction of robotic prostatectomy has not reduced PPI[6]. Effective methods to reduce PPI are a priority.

Pelvic floor muscle training (PFMT) to enhance muscular control of urinary continence after prostatectomy is logical. Although efficacy of PFMT in female stress urinary incontinence has class 1 evidence[7], early optimistic outcomes for PPI[8] are superseded by systematic review evidence of no efficacy in males[9]. Recent physiological research using innovative ultrasound imaging[10 11] and electromyography methods[12] suggests that conventional PFMT programs, which involves repeated maximal contractions assessed by digital rectal examination, and commenced after surgery[13]; fail to consider the mechanisms of incontinence after prostatectomy; are unlikely to target the muscles that control urinary continence; do not target the aspects of function that need to be trained; and start too late.

Urinary continence in men depends on contributions from smooth muscle of the urethra and urethral constriction generated by contraction of three striated muscles: the striated urethral sphincter (SUS); puborectalis/pubovisceralis (PR); and bulbocavernosus (BC)[10]. These striated muscles maintain gentle activation during urine storage[12 14] with additional activation when continence is challenged by elevated intra-abdominal pressure

such as coughing[15] or postural tasks[14]. Radical prostatectomy inherently removes the prostatic segment of the urethra, and its smooth muscle (called the internal sphincter), and may remove/damage the SUS muscle[16] or its innervation[17]. Surgery may also affect the smooth muscle of the bladder neck[17], as well as bladder contractility[18] and compliance[16], contributing to overactivity of the detrusor muscle[16 18]. Recovery of continence after prostatectomy is likely to require: enhanced function of SUS (and other striated muscles) to compensate for the reduced smooth muscle; compensation by the PR and BC if SUS is affected by surgery; and training of the bladder to hold volume. Recent work has highlighted that persistent PPI is associate with impaired shortening of the SUS and BC, and descent rather than elevation of the bladder neck (explained by failure of PR to prevent depression from excessive abdominal pressure) during voluntary activation, but this varies between men[10].

Supported by this physiological evidence and pilot clinical data, we predict that by implementation of a PFMT program that targets the muscles that control urethral pressure (particularly SUS) and compensates for tissues removed during surgery, in a manner that matches the individual needs of each man, and trains incorporation of pelvic floor muscle activation into functional tasks, we can achieve superior outcomes with substantial impact on quality of life after prostatectomy.

Aim

In this trial we aim to:

1. Determine whether PFMT that involves individualised functional training of neuromuscular (NM) control of striated muscles that constrict the urethra (*Urethral training*) achieves more rapid continence recovery after radical prostatectomy than a PFMT program that involves brief strong contractions of muscles around the anus that are not specific for urinary continence (*Conventional training)* or *No training.*

2. Test whether the quality of NM control of striated muscles that constrict the urethra at baseline (prior to surgery) moderates the relative efficacy of *Urethral training* compared to *Conventional training* or *No training*.
3. Determine whether change in NM control of striated muscles that constrict the urethra mediates the recovery of urinary continence.
4. Compare the cost effectiveness of the training programs.

Methods and analysis

Study design

This manuscript describes a research protocol for the "personalised pelvic floor Muscle Training for Urinary incontinence after Prostatectomy" (MaTchUP) randomised controlled trial. This study is a prospectively registered, randomised controlled trial. Participants will be randomised into either *Urethral training, Conventional training* or *No training*. This protocol has been developed in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)[19].

Participant recruitment

Men scheduled to undergo radical prostatectomy (open or robotic) for prostate cancer at the Wesley and Princess Alexandra Hospitals (Brisbane, Queensland) will be invited to participate via an information pamphlet provided by administrative staff during a pre-surgical consultation with their treating urologist.

Participants

To be eligible, participants must meet the following criteria:

Inclusion criteria:

- Scheduled to undergo radical prostatectomy for prostate cancer,

- 30–70 years of age,
- Able to attend assessment/rehabilitation sessions in Brisbane,
- Able to understand English.

Exclusion criteria:

- Urinary incontinence prior to surgery,
- Previous prostate surgery,
- Assessment/training of the pelvic floor muscles in the preceding 6 months,
- Scheduled to undergo or had previously undergone radiation therapy for prostate cancer.

Study Treatments

Volunteers will be screened via an on-line form and phone interview and then scheduled to undergo a baseline assessment in the laboratory 1-2 weeks prior to surgery. After baseline assessment, participants will be randomised into one of three groups: *Conventional training*, *Urethral training* or *No training*.

Randomisation will be in permuted blocks of size 4-8, stratified by surgeon and baseline NM control of striated muscles that constrict the urethra with patients dichotomised as good [or poor] by ability to achieve both ≥4.1 mm of SUS displacement and ≥2.4 mm of PR displacement as assessed with transperineal ultrasound imaging (see below; Stafford et al., 2018 unpublished data). Group allocation will be determined using an automatic randomisation schedule developed by an independent statistician and integrated into the REDCap data administration system (see below) to ensure concealed allocation. Participants randomly allocated to the groups receiving treatment will attend up to 10 treatment sessions supervised by a physiotherapist. All participants will attend an initial session 1-2 weeks before surgery (after the baseline assessment). At this session, participants in the *No training* group will undergo no assessment or training and will not attend further

sessions. Participants allocated to one of the two treatment groups will be assessed by the physiotherapist at the pre-operative session according to their allocated exercise program and taught the initial training exercise to commence prior to surgery. After surgery, participants in the exercise groups will attend up to 9 sessions, 1 week apart, commencing after catheter removal (~2 weeks post-surgery) and continued until continence is achieved (using the definition below) or until 10 sessions have been utilised. Exercise programs will be documented according to the Consensus on Exercise Reporting Template (CERT) guidelines[20] which has been adapted specifically for recording PFMT programs by Hall et al.[21].

Conventional training

The Conventional PFMT is focused on repeated maximal contraction of the muscles around the anus and follows the principles of the program[13] used in the largest previous RCT for men with PPI[22]. Training commences with an assessment of muscle activation (digital rectal examination or anal surface electromyography (EMG)). Participants perform 3-s maximal contractions in lying, sitting and standing, two times per day, and also before activities such as coughing, lifting, rising from sitting. Daily home exercise are encouraged and monitored by a physiotherapist. Training progresses by increasing the duration of contractions, up to 10 s.

Urethral training

Urethral training is an individualised PFMT program focused on the striated pelvic floor muscles that constrict the urethra (SUS, PR, BC) with progression according to a decision tool developed with a Clinical Advisory Committee. Exercise relies on the principles of motor learning, skill training and exercise physiology. Training uses transperineal ultrasound imaging for assessment of pelvic floor muscle activation during voluntary contraction, coughing and a 60-s maximal contraction[11 15 23] to guide treatment tailoring.

Transperineal ultrasound imaging is also used for biofeedback at each physiotherapy session. Urethral training commences with skill acquisition of the optimal pattern of pelvic floor muscle activation to increase urethral pressure and avoidance of excessive abdominal muscle contraction. Initial training focusses on SUS, but with tailoring to include the other muscles, based on the assessment. Progression includes: training for activation of pelvic floor muscles in functional tasks; bladder training to increase holding capacity; sustained holding to enhance adaptation of striated muscles to provide ongoing maintenance of continence; training of ballistic efforts for episodes of increased bladder pressure (lifting, coughing, etc); and high-performance training including strength training to prepare for demanding tasks. Daily home exercise to practice tasks taught in each session will be encouraged and monitored by a physiotherapist.

No training

Participants allocated to *No training* will attend a pre-operative session with a physiotherapist during which they will receive standard written education material (similar to the online-resources readily available from prostate cancer support groups) and education about how to perform the outcome measures.

Participants in all groups will be requested to refrain from seeking additional treatment until the primary end-point at 3 months. Any treatment sought by participants will be recorded.

Physiotherapists will be trained to apply one treatment only. They will have prior experience with management of incontinence and will undergo sufficient training to ensure competence. Therapists providing *Urethral training* will receive comprehensive training in transperineal ultrasound imaging. Competence of therapists will be formally assessed and treatment fidelity evaluated by observation during a subset of sessions by a researcher to document adherence to the protocol.

Data collection

All data will be collected online using REDCap (Research Electronic Data Capture). Participants will complete an online questionnaire at baseline to provide demographic data including date of birth, height, weight, employment status, marital status, education level, smoker status and comorbidities. Prostate volume, Gleason score, surgery date, surgery type, surgery complications, date of catheter removal, and adjunct treatments will also be recorded. Primary and secondary data (except neuromuscular control measures) will be recorded with the online system according to the schedule outlined in Table 1. The primary endpoint at 3 months was selected as qualitative research highlights that rapid/complete recovery of continence is a priority for men[24] as long periods of incontinence have a major impact on quality-of-life[25], and it was considered unethical to withhold treatment from men allocated to *No training* for more than 3 months if they continue to experience incontinence.

Table 1: Data collection timeline

	Enrolment	Baseline	Allocation	Post-Allocation				
Time point		1-2 weeks pre-op		~1 week pre-op	~2 weeks post-op	6 weeks	3 months	12 months
Enrolment:								
Eligibility screen	X							
Informed consent	X							
Randomisation			X					
Interventions:								
Urethral training				←	—	—	→	
Conventional training				←	—	—	→	
No training				X				
Assessments:								
24-hour pad weight test *		X			←	—	X (primary outcome)	X
NM control measure		X			X	X	X	X
ICS-male SF *		X			←	—	X	X
IPAQ *		X			←	—	X	X
SF-12 (weekly)		X			←	—	X	X
EQ-5D-5L (weekly)		X			←	—	X	X
Incontinence-related costs *		X			←	—	X	X
Sexual function (weekly)		X			←	—	X	X
Bowel function (weekly)		X			←	—	X	X
Treatment adherence (monthly)					←	—	X	X

NM = neuromuscular; ICS-male SF = International Continence Society Male Short Form; SF-12 = 12-item Short Form Survey; EQ-5D-5L = 5 level EuroQol 5 dimension, IPAQ = International Physical Activity Questionnaire; * = weekly to primary end-point at 3 months, then monthly to 12 months

For secondary outcome measures of NM control, participants will attend laboratory sessions at baseline (prior to randomisation for identification of NM control parameters used for stratification and as moderator of treatment efficacy), ~2 weeks post-op after catheter removal (for secondary analysis of post-op NM control as a moderator of treatment efficacy), 6 weeks (for intermediate measurement of NM control to judge improvement in NM control

as a potential causal mediator of outcome) and 12 months (for secondary analysis of long-term outcome of intervention) (Table 1).

Secondary outcomes (continence [continence questionnaire and 24-hour pad test], physical activity, quality of life, incontinence-related costs, and sexual function and bowel function) will be entered into the online data management system weekly until the primary end point at 3 months. All secondary outcomes will also be collected at 12 months. All men will continue to complete the continence [continence questionnaire and 24-hour pad test], physical activity, and incontinence-related costs data monthly until 12 months. Men will be prompted to complete this information via their preferred method (SMS, telephone or e-mail).

Treatment adherence

Adherence to exercise will be encouraged by the treating physiotherapist and monitored using an online questionnaire. Physiotherapists will be trained to promote adherence to the program using principles of behaviour change including identification of barriers, cognitive analysis, prioritisation and action planning. Participants will be prompted monthly via their preferred method (SMS, telephone or e-mail) to input data of home exercise performance. This was selected rather than weekly measurement to avoid excessive prompting of the *No treatment* group.

Blinding

Assessors and statisticians will be blinded to group allocation. It will not be possible to blind the participant or treating therapist to the treatment, but patients will be blinded to the hypotheses or details of treatments applied to other groups. Prior to randomisation participants will be informed that systematic reviews show uncertain evidence of benefit from PFMT (note that all men, including the *No treatment* group, will receive written information about PFMT).

Outcome measures

Primary Outcome

The primary outcome measure will be the 24-hour pad weight test. It will be assessed at baseline and 3 months. Continence is defined as a loss of <2g of urine[8]. The day before laboratory testing, the SMS service will remind men to pre-weigh and retain all pads used for the next 24 hours in sealed plastic bags and weigh them using provided scales. Data will be provided to the research staff at the laboratory session. The dichotomous classification of continence will be the primary outcome, and the measure of pad weight (grams) recorded as a secondary outcome.

Secondary outcomes

Ultrasound measures of NM control of urethral pressure: NM control of pelvic floor muscles will be assessed at baseline, post-surgery, 6 weeks, 3 months and 12 months during: (i) voluntary contraction of pelvic floor muscles; (ii) cough according to a protocol described by Stafford et al.[11]; (iii) maximal voluntary contraction sustained for 60 s, and (iv) repeated contractions. These measures have been validated as measure of activation of the individual pelvic floor muscles[23].

Other secondary outcomes that will be measured as outlined in Table 1 are;

(i) International Continence Society Male Short Form (incontinence subscale) (ICS-male SF): Measures the symptomatology and "bothersomeness" of incontinence for men with prostatic disease.

(ii) Self-assessed 24-hour pad test: So that the test can be completed at home, men will be provided with a digital scale to weigh all pads used in a 24-hour period. The start and end of the test will be prompted using the SMS service and a bladder diary will be collected for this period.

(iii) International Physical Activity Questionnaire (IPAQ): Used to assess physical activity over the same period as the 24-hour pad weight test.

(iv) 12-Item Short Form Survey (SF-12)[26]: Used to measure health-related quality of life based on recommendations of a recent systematic review of quality-of-life measures for prostate cancer[27]. The SF-6D computation may also be applied to SF-12 data to compute the utility weights required to construct Quality-Adjusted Life-Year (QALY) measures for use in the cost-effectiveness analysis.

(v) EQ-5D-5L[28]: Used to calculate the QALY saved for cost-effectiveness analysis.

(vi) Incontinence-related costs (use of health services/devices): Recorded prospectively for every participant for 12 months. Men will be prompted to input data using the data collection system. Data will include visits to health care practitioners (e.g. therapists, GP), drugs, and number of devices such as pads or bed/chair protectors used.

(vii) Sexual function: Determined using the question "Are you currently able to achieve a full erection?".

(viii) Bowel function: Determined using questions previously described in a clinical trial of post-prostatectomy incontinence[29].

Data Integrity

All data will be directly collected into the REDCap Electronic Data Capture program. Any inconsistencies in the data will be explored and resolved. The database will be backed-up regularly on a secure network and be compliant to the ICH Guideline for Good Clinical Practice[30], according to our Data Management Plan. Study personnel will only be able to access the database with a personal login and password.

Retention of documents

Study investigators will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After completion of the study, study data will be archived by The University of Queensland for a minimum of 15 years.

Data analysis

Primary endpoint and sample size justification

The primary outcome is the proportion of participants continent at 3 months. This study is powered to determine whether the *Urethral training* is more efficacious than *Conventional training*. This difference is expected to be smaller than the difference between *Urethral* and *No training*. Data from seven RCTs (see [31]) indicate ~60% of men receiving *Conventional training* will be incontinent at 3 months. With 97 men per group, a reduction of incontinence by a third to 40% of men at 3 months (conservatively based on the difference identified in a previous study [8], which included some features we consider critical in the proposed program) can be detected with 80% power and a two-sided significance level of 0.05

Our data of healthy men suggest ~55% have good baseline NM control (Stafford et al., 2018 unpublished data), defined as ability to achieve both ≥4.1 mm of SUS displacement and ≥2.4 mm of PR displacement as assessed with transperineal ultrasound imaging during voluntary contraction (Stafford et al., 2018 unpublished data). We make the assumption that among those with good baseline NM control, incontinence outcomes at 3 months will be similar regardless of treatment arm. With these assumptions and sample size, we have 88% power to detect a significant interaction between baseline NM control and treatment arm if we assume that 70% of men with good baseline NM control will be continent at 3 months regardless of treatment, but that, of the men with poor baseline NM control, 90% and 50%

will be continent with *Urethral* or *Conventional training*, respectively. We will recruit 121 men per arm (adjusting for a potential drop-out rate of 20%). This is feasible based on a recent RCT of 308 participants[6] from a subset of our referral sources.

Statistical analysis

A biostatistician (JK) will analyse blinded data, with all patients enrolled and randomised to treatment/no treatment arms comprising the data set for analysis. Baseline characteristics of groups will be tabulated using summary statistics. If required, multiple imputation will be used to account for missing data, with imputation conducted separately for each treatment arm.

Primary analysis

Analyses will be by intention-to-treat of all randomised participants. For the binary continence outcome, a hierarchical logistic regression model including random effects to account for multiple measurements per participant, and random effects for physiotherapists, will be fit. This model will include a three-way interaction term between time, randomised treatment group, and baseline NM control, and all 2-way interactions and main effects, as well as 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 intervals[32]. 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. Post-operative NM control measures will be considered in a secondary analysis.

Secondary analyses

The continuous measure of continence (24-hour pad test – pad weight) and other continuous outcomes (ICS-male SF, SF12, EQ-5D-5L, sexual function, and bowel function) will be compared between groups by fitting similar random effects linear regression models.

Time to recovery of continence will be compared between groups using a Cox proportional hazards model using the weekly self-assessed pad test. Model assumptions (linearity, normality and homoscedasticity of residuals for the linear regression models, and proportional hazards) will be assessed using standard diagnostic plots.

Mediation analysis: To determine the extent to which the effect of *Urethral training* on the primary outcome and on the continuous measurement of continence is mediated through an improvement in NM control, as hypothesised, we will apply a causal mediation analysis[33]. Mediation analyses will be conducted treating the 6-week and 3-month NM control measures as the potential mediators, with all analyses adjusted for baseline NM control and other potential confounders of the outcome-mediator relationship (e.g. prostate volume, Gleason score, age, etc.). The analysis will be conducted in two stages: at the first stage, the effect of randomisation to the study arms on NM control measures will be assessed. In the second stage, models will be fit to estimate the direct effect of randomised group on outcome and the indirect effect of randomised group on the outcome that acts through the putative mediator. Whether the indirect effect of treatment on the outcomes changes depending on the level of NM control achieved after surgery will be investigated through the inclusion of interaction terms between treatment group and post-surgery NM control variables in the mediation analyses.

If significant mediation is found, logistic regression will be undertaken using the 3-month data of the NM control variables to determine which variables are best linked with continence. A factor analysis across all participants will be applied to extract common NM control features from the NM control variables. NM control features will then be used as predictor variables in the logistic regression analysis to assess the relative contribution of each to the odds of regaining continence.

Cost effectiveness analysis: Costs of services and devices will be estimated using market prices. We will undertake two analyses. First, we will compare cost-effectiveness between treatment arms (3- and 12-month data). Second, we will address the question of whether treatment is more cost-effective if only offered to men with poor NM control at baseline. For this analysis we will test the interaction between treatment arm and baseline NM control. This will test the hypothesis that continence-related costs will be similar for men with good NM control, regardless of treatment allocation, but costs will be significantly less for men with poor baseline NM control allocated to *Urethral training*. Quality-adjusted life-years saved (QALYs) will be computed using the EQ-5D-5L data and SF-12 data, using an SF6D algorithm. Cost-effectiveness ratios will be computed and n-way sensitivity analyses will be conducted to produce cost-effectiveness acceptability curves for relevant sets of assumptions about costs and outcomes.

Contamination between groups

We do not anticipate contamination between *Urethral training* and *Conventional training* as different therapists will apply each intervention. Further, ultrasound imaging is required for the *Urethral training* and is not available to the other groups. It is possible that men allocated to *No treatment* will be exposed to information regarding PFMT (in addition to that provided to them in written form at the pre-surgery visit to the physiotherapist) through searching the internet and from friends and family. However, evidence from several trials shows that provision of information alone does not lead to clinical improvement[31].

Ethics and dissemination

This study is supported by grants from the National Health and Medical Research Council of Australia and Queensland Health, is registered with the Australian New Zealand Clinical Trials Registry, and has ethical approval from the Human Research Ethics Committees of The University of Queensland (2017001736), Uniting Care

(UCHHREC1739), and Metro South (HREC/17/QPAH/591)(Table 2). The funders have not contributed to the design of the trial, nor will they be involved in its conduct or management. The current protocol is version 2 (2nd May 2018) and any future protocol modifications would require approval by the principal investigator (PWH) and formal amendment.

Table 2: Trial registration data

Data category	Information
Primary registry and trial identifying number	Australia New Zealand Clinical Trials Registry [ACTRN12617000788370]
Date of registration in primary registry	30/05/2017
Secondary identifying numbers	Universal Trial Number U1111-1196-7696
Sources of monetary or material support	Sponsors (below)
Primary sponsor	National Health and Medical Research Council - Research Committee Secretariat NHMRC, GPO Box 1421, Canberra, ACT 2601
Secondary sponsor	Queensland Health Physiotherapy Research Fellowship - Queensland Health Building 147-163 Charlotte Street, Brisbane, Queensland 4000
Contact for public queries	RS (r.stafford@uq.edu.au)
Contact for scientific queries	RS (r.stafford @uq.edu.au)
Public title	Personalised pelvic floor Muscle Training for Urinary incontinence after Prostatectomy

Scientific title	Efficacy of a personalised pelvic floor Muscle Training program on Urinary incontinence after radical Prostatectomy: A randomised clinical trial with embedded physiological studies
Countries of recruitment	Australia
Health condition or problem studied	Post-prostatectomy incontinence
Intervention	Urethral muscle training - comprehensive individualized program focused on training the striated muscles that pressurise the urethra.
Key inclusion and exclusion criteria	Inclusion criteria: aged 30 to 70 years; scheduled to undergo radical prostatectomy for prostate cancer; able to attend assessment and treatment sessions; able to understand English
	Exclusion criteria: urinary incontinence prior to surgery; previous prostate/urethral surgery; assessment/training of pelvic floor muscles in preceding 6 months; scheduled to undergo or had previously undergone radiation therapy for prostate cancer.
Study type	Randomised controlled trial, assessor and statistician blinding, automatic independent randomisation
Date of first enrolment	27/07/2018
Target sample size	363
Recruitment status	Recruiting

Primary outcome(s)	Continence defined by the 24-hour pad weight test
Key secondary outcomes	12-Item Short Form Survey (SF-12); International Continence Society Male Short Form Questionnaire; Continence-related costs; 24-hour pad test; Measures of neuro-muscular control of urethral pressure; International Physical Activity Questionnaire (IPAQ); EQ-5D-5L questionnaire; Questions related to sexual and bowel function

Potential participants will be invited to participate via their treating urologist. To manage this unequal relationship, potential participants will be informed that trial assessments and interventions are not part of their routine care, that they are free to decide to participate without coercion, and that the decision to not participate will not influence their management or relationship with their urologist. Although the urologist may discuss the trial with the patient, they will not be involved in the screening or consent process, nor any of the assessment or training sessions.

As standard practice at the Princess Alexandra Hospital involves provision of written information only, no treatment will be withheld from patients. If a patient continues to experience incontinence at the completion of the primary endpoint we will provide them with information of treatment options.

Participants will be given contact details of the project manager for queries or concerns. As all treatments are low risk no adverse events are anticipated, but if any do occur they will be recorded and reported. Records of complaints arising from the trial will be acted upon in accordance with institutional policy. Participants will be informed they are free to

withdraw from the study at any time. They will be given the option to receive the results of the study in summary format at the conclusion of the trial.

Participant data sheets will be stored in a locked cabinet, in addition to electronic storage of scanned copies on the secure institutional data server. All other data will be stored in electronic format in a de-identified manner. Consent forms (that include both a code and identifiable information) will be stored separately to the coded data in a locked cabinet. The data collected in this trial will be thoroughly analysed and published. As this data will be specific to the interventions provided, we do not anticipate any secondary use of the information. The trial consent form includes the option to opt out of making data available for future analyses.

The results will be disseminated through publication in peer-reviewed scientific journals and presented at major international scientific meetings. Further, the study outcomes will be disseminated to the broader community through paper-based and online media.

Authors' contributions

All authors have contributed to the design of the trial and preparation of the protocol manuscript.

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Competing interests statement

No authors have any competing interests to declare.

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	19
Protocol version	3	Date and version identifier	19
Funding	4	Sources and types of financial, material, and other support	19, 22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, 21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of a personalised pelvic floor Muscle Training program on Urinary incontinence after radical Prostatectomy (MaTchUP): Protocol for a randomised controlled trial

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Efficacy of a personalised pelvic floor Muscle Training program on Urinary incontinence after radical Prostatectomy (MaTchUP): Protocol for a randomised controlled trial

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Abstract

Introduction: Prostate cancer is the most common cancer in men. Prostatectomy is the most common treatment. Morbidity from prostatectomy is high - 80% of men experience urinary incontinence which negatively impacts quality-of-life. Post-surgical pelvic floor muscle training is commonly prescribed but recent systematic reviews found no evidence of efficacy. We propose a new treatment that commences pre-operatively and targets functional training of specific pelvic floor muscles that contribute to urinary continence. Assessment and biofeedback using transperineal ultrasound imaging assists training. This will be compared against conventional training (maximal pelvic floor muscle contraction assessed by digital rectal examination), and no training. Embedded physiological studies will allow the investigation of moderation and mediation of the treatment effect on the outcomes.

Methods and analysis: This randomised clinical trial will include 363 men scheduled to undergo radical prostatectomy for prostate cancer. Participants will be randomised into *Urethral training*, *Conventional training*, and *No training* groups. Clinical data will be collected at baseline (1-2 weeks pre-surgery), and post-surgery after catheter removal, weekly to 3 months (primary endpoint), and monthly to 12 months. Outcomes include 24-hour pad weight test (primary), incontinence, quality-of-life and cost effectiveness data. Neuromuscular control measures of pelvic floor muscles will be measured at baseline, post-surgery, 6 weeks, 3 and 12 months. Study assessors and statistician will be blinded to the group allocation.

Ethics and dissemination: This study is registered with the Australian New Zealand Clinical Trials Registry and has ethical approval from university and host hospital Ethics Committees.

Trial outcomes will be shared via national/international conference presentations and peer-reviewed journal publications.

Trial registration number: ACTRN12617000788370 (registered 30th May 2017)

Article Summary

Strengths and limitations of the study

- Uses randomised design in a clearly defined population
- Tests an innovative intervention designed to target mechanisms of urinary continence in men that is based on recent physiological data of mechanisms of continence and incontinence in men
- Uses individualised care based on assessment using new transperineal ultrasound imaging methods to study pelvic floor muscle function
- Includes investigation of mediation and moderation of the treatment effect by pelvic floor muscle neuromuscular control variables
- Possible limitations are adherence to the comprehensive home program and the burden of the extensive follow-up data collection

Introduction

Prostate cancer is the most common non-cutaneous cancer in men in Australia and internationally (1 in 7 men) and the second most common cause of cancer death[1]. Radical prostatectomy (prostate removal to prevent metastasis) is a common treatment. The good news is that prostate cancer has very high 5-yr survival - 95%[1]. The bad news is that morbidity is high – almost 80% of men experience incontinence after prostatectomy (post-prostatectomy incontinence: PPI)[2], and many are incontinent beyond 12 months[2]. PPI has been identified as the major determinant of quality of life for these men, and many live for many years with ongoing major cost (up to 33% use incontinence products[3]) and social isolation[4 5]. Introduction of robotic prostatectomy has not reduced PPI[6]. Effective methods to reduce PPI are a priority.

Pelvic floor muscle training (PFMT) to enhance muscular control of urinary continence after prostatectomy is logical. Although efficacy of PFMT in female stress urinary incontinence has class 1 evidence[7], early optimistic outcomes for PPI[8] are superseded by systematic review evidence of no efficacy in males[9]. Recent physiological research using innovative ultrasound imaging[10 11] and electromyography methods[12] suggests that conventional PFMT programs, which involves repeated maximal contractions assessed by digital rectal examination, and commenced after surgery[13]; fail to consider the mechanisms of incontinence after prostatectomy; are unlikely to target the muscles that control urinary continence; do not target the aspects of function that need to be trained; and start too late.

Urinary continence in men depends on contributions from smooth muscle of the urethra and urethral constriction generated by contraction of three striated muscles: the striated urethral sphincter (SUS); puborectalis/pubovisceralis (PR); and bulbocavernosus (BC)[10]. These striated muscles maintain gentle activation during urine storage[12 14] with additional activation when continence is challenged by elevated intra-abdominal pressure

such as coughing[15] or postural tasks[14]. Radical prostatectomy inherently removes the prostatic segment of the urethra, and its smooth muscle (called the internal sphincter), and may remove/damage the SUS muscle[16] or its innervation[17]. Surgery may also affect the smooth muscle of the bladder neck[17], as well as bladder contractility[18] and compliance[16], contributing to overactivity of the detrusor muscle[16 18]. Recovery of continence after prostatectomy is likely to require: enhanced function of SUS (and other striated muscles) to compensate for the reduced smooth muscle (which would require capacity for low intensity sustained contraction in addition to strong contraction); compensation by the PR and BC if SUS is affected by surgery; and training of the bladder to hold volume. Recent work has highlighted that persistent PPI is associate with impaired shortening of the SUS and BC, and descent rather than elevation of the bladder neck (explained by failure of PR to prevent depression from excessive abdominal pressure) during voluntary activation, but this varies between men[10]. Digital rectal examination used for assessment and feedback in most previous trials of PFMT for incontinence after prostatectomy[19] 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 validated[20] method to evaluate and provide feedback of PR, SUS and BC, simultaneously.

Supported by this physiological evidence and pilot clinical data, we predict that by implementation of a PFMT program that targets the muscles that control urethral pressure (particularly SUS) and compensates for tissues removed during surgery, in a manner that matches the individual needs of each man, and trains incorporation of pelvic floor muscle activation into functional tasks (rather than a training program limited to repeated maximal voluntary contractions), we can achieve superior outcomes with substantial impact on quality of life after prostatectomy.

Aim

In this trial we aim to:

1. Determine whether PFMT that involves individualised functional training of neuromuscular (NM) control of striated muscles that constrict the urethra (*Urethral training*) achieves more rapid continence recovery after radical prostatectomy than a PFMT program that involves brief strong contractions of muscles around the anus that are not specific for urinary continence (*Conventional training)* or *No training.*
2. Test whether the quality of NM control of striated muscles that constrict the urethra at baseline (prior to surgery) moderates the relative efficacy of *Urethral training* compared to *Conventional training* or *No training*.
3. Determine whether change in NM control of striated muscles that constrict the urethra mediates the recovery of urinary continence.
4. Compare the cost effectiveness of the training programs.

Methods and analysis

Study design

This manuscript describes a research protocol for the "personalised pelvic floor Muscle Training for Urinary incontinence after Prostatectomy" (MaTchUP) randomised controlled trial. This study is a prospectively registered, randomised controlled trial. Participants will be randomised into either *Urethral training, Conventional training* or *No training*. This protocol has been developed in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)[21].

Participant recruitment

Men scheduled to undergo radical prostatectomy (open or robotic) for prostate cancer at the Wesley and Princess Alexandra Hospitals (Brisbane, Queensland) will be invited to participate via an information pamphlet provided by administrative staff during a pre-surgical consultation with their treating urologist.

Participants

To be eligible, participants must meet the following criteria:

Inclusion criteria:

- Scheduled to undergo radical prostatectomy for prostate cancer,
- 30–70 years of age,
- Able to attend assessment/rehabilitation sessions in Brisbane,
- Able to understand English.

Exclusion criteria:

- Urinary incontinence prior to surgery,
- Previous prostate surgery,
- Assessment/training of the pelvic floor muscles in the preceding 6 months,
- Scheduled to undergo or had previously undergone radiation therapy for prostate cancer.

Study Treatments

Volunteers will be screened via an on-line form and phone interview and then scheduled to undergo a baseline assessment in the laboratory 1-2 weeks prior to surgery. After baseline assessment, participants will be randomised into one of three groups: *Conventional training*, *Urethral training* or *No training*.

Randomisation will be in permuted blocks of size 4-8, stratified by surgeon and baseline NM control of striated muscles that constrict the urethra with patients dichotomised

as good [or poor] by ability to achieve both ≥4.1 mm of SUS displacement and ≥2.4 mm of PR displacement as assessed with transperineal ultrasound imaging (see below; Stafford et al., 2018 unpublished data). Group allocation will be determined using an automatic randomisation schedule developed by an independent statistician and integrated into the REDCap data administration system (see below) to ensure concealed allocation. Participants randomly allocated to the groups receiving treatment will attend up to 10 treatment sessions supervised by a physiotherapist. All participants will attend an initial session 1-2 weeks before surgery (after the baseline assessment). At this session, participants in the *No training* group will undergo no assessment or training and will not attend further sessions. Participants allocated to one of the two treatment groups will be assessed by the physiotherapist at the pre-operative session according to their allocated exercise program and taught the initial training exercise to commence prior to surgery. After surgery, participants in the exercise groups will attend up to 9 sessions, 1 week apart, commencing after catheter removal (~2 weeks post-surgery) and continued until continence is achieved (using the definition below) or until 10 sessions have been utilised. Exercise programs will be documented according to the Consensus on Exercise Reporting Template (CERT) guidelines[22] which has been adapted specifically for recording PFMT programs by Hall et al.[23].

Conventional training

The Conventional PFMT is focused on repeated maximal contraction of the muscles around the anus and follows the principles of the program[13] used in the largest previous RCT for men with PPI[24]. Training commences with an assessment of muscle activation (digital rectal examination or anal surface electromyography (EMG)). Participants perform 3-s maximal contractions in lying, sitting and standing, two times per day, and also before activities such as coughing, lifting, rising from sitting. Daily home exercise are encouraged

and monitored by a physiotherapist. Training progresses by increasing the duration of contractions, up to 10 s.

Urethral training

Urethral training is an individualised PFMT program focused on the striated pelvic floor muscles that constrict the urethra (SUS, PR, BC) with progression according to a decision tool developed with a Clinical Advisory Committee. Exercise relies on the principles of motor learning, skill training and exercise physiology. Training uses transperineal ultrasound imaging for assessment of pelvic floor muscle activation during voluntary contraction, coughing and a 60-s maximal contraction[11 15 20] to guide treatment tailoring. Transperineal ultrasound imaging is also used for biofeedback at each physiotherapy session. Urethral training commences with skill acquisition of the optimal pattern of pelvic floor muscle activation to increase urethral pressure and avoidance of excessive abdominal muscle contraction. Initial training focusses on SUS, but with tailoring to include the other muscles, based on the assessment. Progression includes: training for activation of pelvic floor muscles in functional tasks; bladder training to increase holding capacity; sustained holding to enhance adaptation of striated muscles to provide ongoing maintenance of continence; training of ballistic efforts for episodes of increased bladder pressure (lifting, coughing, etc); and high-performance training including strength training to prepare for demanding tasks. Daily home exercise to practice tasks taught in each session will be encouraged and monitored by a physiotherapist.

No training

Participants allocated to *No training* will attend a pre-operative session with a physiotherapist during which they will receive standard written education material (similar to the online-resources readily available from prostate cancer support groups) and education about how to perform the outcome measures.

Participants in all groups will be requested to refrain from seeking additional treatment until the primary end-point at 3 months. Any treatment sought by participants will be recorded.

Physiotherapists will be trained to apply one treatment only. They will have prior experience with management of incontinence and will undergo sufficient training to ensure competence. Therapists providing *Urethral training* will receive comprehensive training in transperineal ultrasound imaging. Competence of therapists will be formally assessed and treatment fidelity evaluated by observation during a subset of sessions by a researcher to document adherence to the protocol.

Data collection

All data will be collected online using REDCap (Research Electronic Data Capture). Participants will complete an online questionnaire at baseline to provide demographic data including date of birth, height, weight, employment status, marital status, education level, smoker status and comorbidities. Prostate volume, Gleason score, surgery date, surgery type, surgery complications, date of catheter removal, and adjunct treatments will also be recorded. Primary and secondary data (except neuromuscular control measures) will be recorded with the online system according to the schedule outlined in Table 1. The primary endpoint at 3 months was selected as qualitative research highlights that rapid/complete recovery of continence is a priority for men[25] as long periods of incontinence have a major impact on quality-of-life[26], and it was considered unethical to withhold treatment from men allocated to *No training* for more than 3 months if they continue to experience incontinence.

Table 1: Data collection timeline

	Enrolment	Baseline	Allocation	Post-Allocation				
Time point		1-2 weeks pre-op		~1 week pre-op	~2 weeks post-op	6 weeks	3 months	12 months
Enrolment:								
Eligibility screen	X							
Informed consent	X							
Randomisation			X					
Interventions:								
Urethral training				←	—	—	→	
Conventional training				←	—	—	→	
No training				X				
Assessments:								
24-hour pad weight test *		X			←	—	X (primary outcome)	X
NM control measure		X			X	X	X	X
ICS-male SF *		X			←	—	X	X
IPAQ *		X			←	—	X	X
SF-12 (weekly)		X			←	—	X	X
EQ-5D-5L (weekly)		X			←	—	X	X
Incontinence-related costs *		X			←	—	X	X
Sexual function (weekly)		X			←	—	X	X
Bowel function (weekly)		X			←	—	X	X
Treatment adherence (monthly)					←	—	X	X

NM = neuromuscular; ICS-male SF = International Continence Society Male Short Form; SF-12 = 12-item Short Form Survey; EQ-5D-5L = 5 level EuroQol 5 dimension, IPAQ = International Physical Activity Questionnaire; * = weekly to primary end-point at 3 months, then monthly to 12 months

For secondary outcome measures of NM control, participants will attend laboratory sessions at baseline (prior to randomisation for identification of NM control parameters used for stratification and as moderator of treatment efficacy), ~2 weeks post-op after catheter removal (for secondary analysis of post-op NM control as a moderator of treatment efficacy), 6 weeks (for intermediate measurement of NM control to judge improvement in NM control

as a potential causal mediator of outcome) and 12 months (for secondary analysis of long-term outcome of intervention) (Table 1).

Secondary outcomes (continence [continence questionnaire and 24-hour pad test], physical activity, quality of life, incontinence-related costs, and sexual function and bowel function) will be entered into the online data management system weekly until the primary end point at 3 months. All secondary outcomes will also be collected at 12 months. All men will continue to complete the continence [continence questionnaire and 24-hour pad test], physical activity, and incontinence-related costs data monthly until 12 months. Men will be prompted to complete this information via their preferred method (SMS, telephone or e-mail).

Treatment adherence

Adherence to exercise will be encouraged by the treating physiotherapist and monitored using an online questionnaire. Physiotherapists will be trained to promote adherence to the program using principles of behaviour change including identification of barriers, cognitive analysis, prioritisation and action planning. Participants will be prompted monthly via their preferred method (SMS, telephone or e-mail) to input data of home exercise performance. This was selected rather than weekly measurement to avoid excessive prompting of the *No treatment* group.

Blinding

Assessors and statisticians will be blinded to group allocation. It will not be possible to blind the participant or treating therapist to the treatment, but patients will be blinded to the hypotheses or details of treatments applied to other groups. Prior to randomisation participants will be informed that systematic reviews show uncertain evidence of benefit from PFMT (note that all men, including the *No treatment* group, will receive written information about PFMT).

Outcome measures

Primary Outcome

The primary outcome measure will be the 24-hour pad weight test. It will be assessed at baseline and 3 months. Continence is defined as a loss of <2g of urine[8]. The day before laboratory testing, the SMS service will remind men to pre-weigh and retain all pads used for the next 24 hours in sealed plastic bags and weigh them using provided scales. Data will be provided to the research staff at the laboratory session. The dichotomous classification of continence will be the primary outcome.

Secondary outcomes

Ultrasound measures of NM control of urethral pressure: NM control of pelvic floor muscles will be assessed at baseline, post-surgery, 6 weeks, 3 months and 12 months during: (i) voluntary contraction of pelvic floor muscles; (ii) cough according to a protocol described by Stafford et al.[11]; (iii) maximal voluntary contraction sustained for 60 s, and (iv) repeated contractions. These measures have been validated as measure of activation of the individual pelvic floor muscles[20].

Other secondary outcomes that will be measured as outlined in Table 1 are;

(i) International Continence Society Male Short Form (incontinence subscale) (ICS-male SF): Measures the symptomatology and "bothersomeness" of incontinence for men with prostatic disease.

(ii) Self-assessed 24-hour pad test: So that the test can be completed at home, men will be provided with a digital scale to weigh all pads used in a 24-hour period. The start and end of the test will be prompted using the SMS service and a bladder diary will be collected for this period. The measure of pad weight (grams) is recorded as the secondary outcome.

(iii) International Physical Activity Questionnaire (IPAQ): Used to assess physical activity over the same period as the 24-hour pad weight test.

(iv) 12-Item Short Form Survey (SF-12)[27]: Used to measure health-related quality of life based on recommendations of a recent systematic review of quality-of-life measures for prostate cancer[28]. The SF-6D computation may also be applied to SF-12 data to compute the utility weights required to construct Quality-Adjusted Life-Year (QALY) measures for use in the cost-effectiveness analysis.

(v) EQ-5D-5L[29]: Used to calculate the QALY saved for cost-effectiveness analysis.

(vi) Incontinence-related costs (use of health services/devices): Recorded prospectively for every participant for 12 months. Men will be prompted to input data using the data collection system. Data will include visits to health care practitioners (e.g. therapists, GP), drugs, and number of devices such as pads or bed/chair protectors used.

(vii) Sexual function: Determined using the question "Are you currently able to achieve a full erection?".

(viii) Bowel function: Determined using questions previously described in a clinical trial of post-prostatectomy incontinence[30].

Data Integrity

All data will be directly collected into the REDCap Electronic Data Capture program. Any inconsistencies in the data will be explored and resolved. The database will be backed-up regularly on a secure network and be compliant to the ICH Guideline for Good Clinical Practice[31], according to our Data Management Plan. Study personnel will only be able to access the database with a personal login and password.

Retention of documents

Study investigators will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After completion of the study, study data will be archived by The University of Queensland for a minimum of 15 years.

Data analysis

Primary endpoint and sample size justification

The primary outcome is the proportion of participants continent at 3 months. This study is powered to determine whether the *Urethral training* is more efficacious than *Conventional training*. This difference is expected to be smaller than the difference between *Urethral* and *No training*. Data from seven RCTs (see [32]) indicate ~60% of men receiving *Conventional training* will be incontinent at 3 months. 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 [8], which included some features we consider critical in the proposed program) can be detected with 80% power and a two-sided significance level of 0.05

Our data of healthy men suggest ~55% have good baseline NM control (Stafford et al., 2018 unpublished data), defined as ability to achieve both ≥4.1 mm of SUS displacement and ≥2.4 mm of PR displacement as assessed with transperineal ultrasound imaging during voluntary contraction (Stafford et al., 2018 unpublished data). We make the assumption that among those with good baseline NM control, incontinence outcomes at 3 months will be similar regardless of treatment arm. With these assumptions and sample size, we have 88% power to detect a significant interaction between baseline NM control and treatment arm if we assume that 70% of men with good baseline NM control will be continent at 3 months regardless of treatment, but that, of the men with poor baseline NM control, 90% and 50%

will be continent with *Urethral* or *Conventional training*, respectively. We will recruit 121 men per arm (adjusting for a potential drop-out rate of 20%). This is feasible based on a recent RCT of 308 participants[6] from a subset of our referral sources.

Statistical analysis

A biostatistician (JK) will analyse blinded data, with all patients enrolled and randomised to treatment/no treatment arms comprising the data set for analysis. Baseline characteristics of groups will be tabulated using summary statistics. If required, multiple imputation will be used to account for missing data, with imputation conducted separately for each treatment arm.

Primary analysis

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 intervals[33]. 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 between time, randomised treatment group, and baseline NM control, and all 2-way interactions and main effects, as well as a term for surgeon.

Secondary analyses

The continuous measure of continence (24-hour pad test – pad weight) and other continuous outcomes (ICS-male SF, SF12, EQ-5D-5L, sexual function, and bowel function) will be compared between groups by fitting similar random effects linear regression models. Time to recovery of continence will be compared between groups using a Cox proportional hazards model using the weekly self-assessed pad test. Model assumptions (linearity, normality and homoscedasticity of residuals for the linear regression models, and proportional hazards) will be assessed using standard diagnostic plots.

Mediation analysis: To determine the extent to which the effect of *Urethral training* on the primary outcome and on the continuous measurement of continence is mediated through an improvement in NM control, as hypothesised, we will apply a causal mediation analysis[34]. Mediation analyses will be conducted treating the 6-week and 3-month NM control measures as the potential mediators, with all analyses adjusted for baseline NM control and other potential confounders of the outcome-mediator relationship (e.g. prostate volume, Gleason score, age, etc.). The analysis will be conducted in two stages: at the first stage, the effect of randomisation to the study arms on NM control measures will be assessed. In the second stage, models will be fit to estimate the direct effect of randomised group on outcome and the indirect effect of randomised group on the outcome that acts through the putative mediator. Whether the indirect effect of treatment on the outcomes changes depending on the level of NM control achieved after surgery will be investigated through the inclusion of interaction terms between treatment group and post-surgery NM control variables in the mediation analyses.

If significant mediation is found, logistic regression will be undertaken using the 3-month data of the NM control variables to determine which variables are best linked with continence. A factor analysis across all participants will be applied to extract common NM control features from the NM control variables. NM control features will then be used as

predictor variables in the logistic regression analysis to assess the relative contribution of each to the odds of regaining continence.

Cost effectiveness analysis: Costs of services and devices will be estimated using market prices. We will undertake two analyses. First, we will compare cost-effectiveness between treatment arms (3- and 12-month data). Second, we will address the question of whether treatment is more cost-effective if only offered to men with poor NM control at baseline. For this analysis we will test the interaction between treatment arm and baseline NM control. This will test the hypothesis that continence-related costs will be similar for men with good NM control, regardless of treatment allocation, but costs will be significantly less for men with poor baseline NM control allocated to *Urethral training*. Quality-adjusted life-years saved (QALYs) will be computed using the EQ-5D-5L data and SF-12 data, using an SF6D algorithm. Cost-effectiveness ratios will be computed and n-way sensitivity analyses will be conducted to produce cost-effectiveness acceptability curves for relevant sets of assumptions about costs and outcomes.

Contamination between groups

We do not anticipate contamination between *Urethral training* and *Conventional training* as different therapists will apply each intervention. Further, ultrasound imaging is required for the *Urethral training* and is not available to the other groups. It is possible that men allocated to *No treatment* will be exposed to information regarding PFMT (in addition to that provided to them in written form at the pre-surgery visit to the physiotherapist) through searching the internet and from friends and family. However, evidence from several trials shows that provision of information alone does not lead to clinical improvement[32].

Ethics and dissemination

This study is supported by grants from the National Health and Medical Research Council of Australia and Queensland Health, is registered with the Australian New Zealand

Clinical Trials Registry, and has ethical approval from the Human Research Ethics Committees of The University of Queensland (2017001736), Uniting Care (UCHHREC1739), and Metro South (HREC/17/QPAH/591)(Table 2). The funders have not contributed to the design of the trial, nor will they be involved in its conduct or management. The current protocol is version 2 (2nd May 2018) and any future protocol modifications would require approval by the principal investigator (PWH) and formal amendment.

Table 2: Trial registration data

Data category	Information
Primary registry and trial identifying number	Australia New Zealand Clinical Trials Registry [ACTRN12617000788370]
Date of registration in primary registry	30/05/2017
Secondary identifying numbers	Universal Trial Number U1111-1196-7696
Sources of monetary or material support	Sponsors (below)
Primary sponsor	National Health and Medical Research Council - Research Committee Secretariat NHMRC, GPO Box 1421, Canberra, ACT 2601
Secondary sponsor	Queensland Health Physiotherapy Research Fellowship - Queensland Health Building 147-163 Charlotte Street, Brisbane, Queensland 4000
Contact for public queries	RS (r.stafford@uq.edu.au)
Contact for scientific queries	RS (r.stafford @uq.edu.au)

Public title	Personalised pelvic floor Muscle Training for Urinary incontinence after Prostatectomy
Scientific title	Efficacy of a personalised pelvic floor Muscle Training program on Urinary incontinence after radical Prostatectomy: A randomised clinical trial with embedded physiological studies
Countries of recruitment	Australia
Health condition or problem studied	Post-prostatectomy incontinence
Intervention	Urethral muscle training - comprehensive individualized program focused on training the striated muscles that pressurise the urethra.
Key inclusion and exclusion criteria	Inclusion criteria: aged 30 to 70 years; scheduled to undergo radical prostatectomy for prostate cancer; able to attend assessment and treatment sessions; able to understand English
	Exclusion criteria: urinary incontinence prior to surgery; previous prostate/urethral surgery; assessment/training of pelvic floor muscles in preceding 6 months; scheduled to undergo or had previously undergone radiation therapy for prostate cancer.
Study type	Randomised controlled trial, assessor and statistician blinding, automatic independent randomisation
Date of first enrolment	27/07/2018

Target sample size	363
Recruitment status	Recruiting
Primary outcome(s)	Continence defined by the 24-hour pad weight test
Key secondary outcomes	12-Item Short Form Survey (SF-12); International Continence Society Male Short Form Questionnaire; Continence-related costs; 24-hour pad test; Measures of neuro-muscular control of urethral pressure; International Physical Activity Questionnaire (IPAQ); EQ-5D-5L questionnaire; Questions related to sexual and bowel function

Potential participants will be invited to participate via their treating urologist. To manage this unequal relationship, potential participants will be informed that trial assessments and interventions are not part of their routine care, that they are free to decide to participate without coercion, and that the decision to not participate will not influence their management or relationship with their urologist. Although the urologist may discuss the trial with the patient, they will not be involved in the screening or consent process, nor any of the assessment or training sessions.

As standard practice at the Princess Alexandra Hospital involves provision of written information only, no treatment will be withheld from patients. If a patient continues to experience incontinence at the completion of the primary endpoint we will provide them with information of treatment options.

Participants will be given contact details of the project manager for queries or concerns. As all treatments are low risk no adverse events are anticipated, but if any do occur they will be recorded and reported. Records of complaints arising from the trial will be acted

upon in accordance with institutional policy. Participants will be informed they are free to withdraw from the study at any time. They will be given the option to receive the results of the study in summary format at the conclusion of the trial.

Participant data sheets will be stored in a locked cabinet, in addition to electronic storage of scanned copies on the secure institutional data server. All other data will be stored in electronic format in a de-identified manner. Consent forms (that include both a code and identifiable information) will be stored separately to the coded data in a locked cabinet. The data collected in this trial will be thoroughly analysed and published. As this data will be specific to the interventions provided, we do not anticipate any secondary use of the information. The trial consent form includes the option to opt out of making data available for future analyses.

The results will be disseminated through publication in peer-reviewed scientific journals and presented at major international scientific meetings. Further, the study outcomes will be disseminated to the broader community through paper-based and online media.

Patient and Public Involvement

The research question was based on hypotheses developed from basic science data, and informed by the poor results reported from previous randomised controlled trials, but did not involve direct patient or public involvement. The primary outcome measure was based on published data of patients' preferences. Patients did not contribute to the design of this study. Patients were not involved in the recruitment to or conduct of the study. The results will be disseminated to study participants in the form of a summary (written in lay language) at the completion of the trial. The acceptability of the nature and burden of the intervention was confirmed by application of the treatment protocol in pilot trials with patients prior to commencement of the study.

Authors' contributions

PH, RS, GC, JAM, AC and LH conceived the study. PH, RS, GC, JK, JAM, AC, LC and LH developed the experimental design for the study. JK designed the statistical analysis of the study and undertook power calculation. LC designed the health economic data collection and analysis. PH, RS, GC, JAM, AC and LC obtained funding for the study. All authors contributed to preparation of the protocol manuscript and all authors approved the final version.

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Competing interests statement

No authors have any competing interests to declare.

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	19
Protocol version	3	Date and version identifier	19
Funding	4	Sources and types of financial, material, and other support	19, 22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 22
	5b	Name and contact information for the trial sponsor	19
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, 21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	22
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	22
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.