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Supervised pelvic floor muscle training versus attention-control massage treatment in patients with faecal incontinence: Statistical analysis plan for a randomised controlled trial

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ABSTRACT

Introduction: Faecal incontinence affects approximately 8–9% of the adult population. The condition is surrounded by taboo; it can have a devastating impact on quality of life and lead to major limitations in daily life. Pelvic floor muscle training in combination with information and fibre supplements is recommended as first-line treatment for faecal incontinence. Despite this, the effect of pelvic floor muscle training for faecal incontinence is unclear. No previous trials have investigated the efficacy of supervised pelvic floor muscle training in combination with conservative treatment and compared this to an attention-control massage treatment including conservative treatment. The aim of this trial is to investigate if 16 weeks of supervised pelvic floor muscle training in combination with conservative treatment is superior to attention-control massage treatment and conservative treatment in patients with faecal incontinence.
Design: Randomised, controlled, superiority trial with two parallel arms.
Methods: 100 participants with faecal incontinence will be randomised to either (1) individually supervised pelvic floor muscle training and conservative treatment or (2) attention-control massage treatment and conservative treatment. The primary outcome is participants' rating of symptom changes after 16 weeks of treatment using the Patient Global Impression of Improvement Scale. Secondary outcomes are the Vaizey Incontinence Score, the Fecal Incontinence Severity Index, the Fecal Incontinence Quality of Life Scale, a 14-day bowel diary, anorectal manometry and rectal capacity measurements. Follow-up assessment at 36 months will be conducted.
Discussion: This paper describes and discusses the rationale, the methods and in particular the statistical analysis plan of this trial.

1. Introduction

Faecal incontinence is the complaint of involuntary loss of faeces [1] and affects approximately 8–9% of the adult population [2,3]. It is a hidden problem – many people are suffering in silence since they are reluctant to reveal their situation [4–7]. The condition can have a devastating impact on quality of life [4,6,8–12] and lead to major limitations in daily life [6,8–11]. In qualitative studies, living with faecal incontinence is described as an everlasting fight for controlling and hiding a condition that is out of control [8–10].

Faecal incontinence is a multifactorial condition. The recommended first-line treatment consists of a multi-modal approach including: information, fibre supplements, antidiarrhoeal medication, laxatives, pelvic floor muscle training (PFMT) and biofeedback training [13–17]. PFMT is defined as 'systematic training with repeated voluntary contractions of the pelvic floor muscles and the external anal sphincter

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; EMG, electromyography; FISI, Fecal Incontinence Severity Index; FIQL, Fecal Incontinence Quality of Life Scale; PFMT, Pelvic floor muscle training; PGI-I, Patient Global Impression of Improvement Scale; SPIRIT, Standard Protocol Items: Recommendation for Interventional Trials; TIDieR, Template for Intervention Description and Replication

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with the purpose of increasing muscle strength, speed, endurance and/or coordination' [13,16,18]. In most trials, PFMT is supplemented with biofeedback training in form of 'strength training' and/or 'rectal sensitivity training' [13,17–19].

A recent systematic Cochrane review [13] included 20 randomised controlled trials to investigate the efficacy of PFMT and/or biofeedback training for the treatment of faecal incontinence in adults. With the exception of two trials that evaluated PFMT and biofeedback training in conjunction with an operation, the included trials compared different training modalities and thus lacked a non-training comparator [13]. This limits the ability to conclude on the 'true' efficacy of PFMT and biofeedback training. Due to risk of bias, intervention heterogeneity and the use of different comparators, the authors of the Cochrane review concluded that the role of PFMT and biofeedback training for treatment of faecal incontinence is unclear [13]. Two trials published after the Cochrane review [20,21] evaluated the effect of PFMT and biofeedback training compared to a group not receiving PFMT. However, neither trial controlled for the possible placebo effect associated with the attention given by the health care professional delivering the training interventions [20,21]. To evaluate the efficacy of PFMT, there is a need for a trial that uses an attention-control treatment, which is biologically ineffective, but controls for the placebo effect associated with the attention given by the health care professional delivering the PFMT. To our knowledge, no previous trials have investigated the efficacy of supervised PFMT in combination with conservative treatment and compared this to an attention-control massage treatment in addition to conservative treatment.

The aim of the current trial is to investigate if supervised PFMT in combination with conservative treatment (mainly information) is superior to attention-control massage-treatment in combination with the same conservative treatment in patients with faecal incontinence. This possible superiority effect is based on the primary outcome of changes in faecal incontinence symptoms after 16 weeks of treatment using The Patient Global Impression of Improvement Scale (PGI-I). The aim of this paper is to describe the rationale, the methods, and in particular the statistical analysis plan of this trial, so that this information is made public.

2. Methods

2.1. Design of the trial

The trial is a prospective, outcome assessor-blinded, randomised, controlled, superiority trial with two parallel arms. Outcome measures will be assessed at baseline (before treatment start) and after 16 weeks of treatment (end of treatment period, primary endpoint) and at a long-term follow-up 36 months after completing the treatments. From January 1, 2016, 98 participants are randomised into two groups (supervised PFMT and attention-control massage treatment) by simple randomisation, using a ratio of 1:1. Data for the primary analysis (baseline plus the 16-week outcome assessment) will be collected from October 24, 2012 until June 17, 2016. Data for the 36-months follow-up will be collected until June 2019. Currently, no analyses have been performed and treatment group allocation remains blinded. This protocol and statistical analysis plan is reported in accordance with the SPIRIT 2013 Statement: Standard Protocol items: Recommendation for Interventional Trials [22] (See the completed SPIRIT checklist attached as Additional file 1). The description of the intervention follows the Template for Intervention Description and Replication (TIDieR) checklist [23]. Once completed, the reporting of the trial will follow the Consolidated Standards of Reporting Trials (CONSORT) checklist [24], using the extension for non-pharmacological interventions [25] supplemented with the TIDieR-checklist for intervention description [23]. The trial was preregistered at ClinicalTrials.gov ID: NCT01705535, https://clinicaltrials.gov/ct2/show/NCT01705535, registration date: October 10, 2012.

2.2. Participants and settings

The trial is ongoing at Copenhagen University Hospital, Hvidovre, Denmark in a collaborative effort between the Department of Physiotherapy- and Occupational Therapy and the Department of Surgical and Medical Gastroenterology. Between October 15, 2012 and December 15, 2015, consecutive patients referred for examination and treatment of faecal incontinence at the Department of Surgical and Medical Gastroenterology will be assessed for eligibility. We aim to include 100 participants, based on estimations described in the 'sample size' section. At the first visit with a specialised nurse, eligible patients will be briefly informed about the trial. Patients interested in the trial will be invited to a second visit at the Department of Physiotherapy- and Occupational Therapy where they will receive thorough verbal and written information about the trial. The enrolment is handled by the primary investigator (AU) who is blinded with respect to allocation to trial arms and not involved in the assessment of outcomes. Before enrolment, the participants will submit written informed consents according to the Declaration of Helsinki.

Inclusion: The inclusion criteria are: faecal incontinence for at least 6 months and age $\geq$18 years.

Exclusion: The exclusion criteria are: pregnancy, chronic diarrhoea, severe neurological disease (Multiple Sclerosis, Parkinson's disease, spinal cord injury, major stroke or neuromuscular junction diseases) rectal prolapse, previous operation for cancer or radiotherapy in the lower abdomen, inadequate Danish, cognitively unable to perform PFMT and more than two sessions of individually supervised PFMT within the last 12 months.

2.3. Randomisation, allocation and concealment

Once included, baseline assessments will be conducted before the participants will be randomised (1:1) to two groups (supervised PFMT or attention-control massage treatment), using simple randomisation (See Fig. 1 for the trial flow). A data manager who has no other involvement in the trial will produce a computer-generated sequence of random group assignments (allocation sequence). The primary investigator (AU) who is blinded to the allocation sequence will enrol the participants. Two secretaries with no other involvement in the trial will manage the allocation sequence and assign the participants to the two groups. The allocation sequence is kept in a locked cabinet and allocation concealment is further secured by the use of sealed, opaque, numbered envelopes prepared by the two secretaries. Finally, participants will be asked repeatedly not to reveal the group allocation to the investigators and outcome assessors.

2.4. Interventions

2.4.1. Conservative treatment program (identical in both trial arms)

Both trial groups will receive a conservative treatment program consisting of standard information and guidance by one of three nurses specialized in faecal incontinence. All three nurses will be blinded to the allocation to trial arms. The program consists of standard advice about diet and fluid intake and the use of fibre supplements. If appropriate, the nurses will inform the participants about optimising bowel-emptying by the use of laxatives with local effect in the rectum (glycerol) and/or use of antidiarrhoeal medication (loperamide). The conservative treatment will be delivered at the first visit to the outpatient clinic at the Department of Surgical and Medical Gastroenterology before inclusion in the trial. The information is followed up by a telephone call by the nurse after approximately one month.

2.4.2. Settings and distribution of interventions

In addition to the conservative treatment program the participants in both groups will receive their allocated intervention treatment. The treatments in both groups will be delivered as individual face-to face

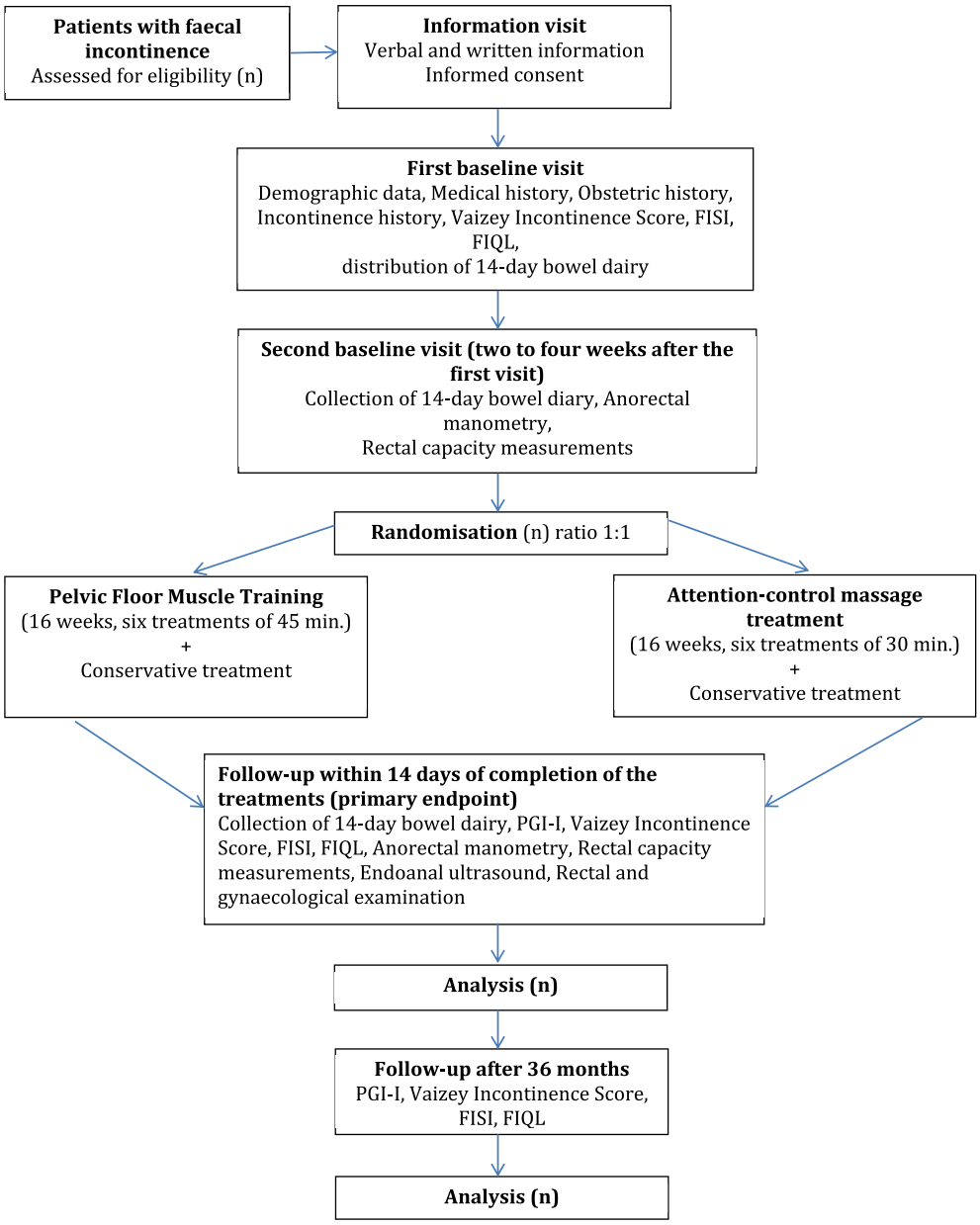

Fig. 1. Trial flow diagram. Abbreviations: FISI: Fecal Incontinence Severity Index, FIQL: Fecal Incontinence Quality of Life Scale; PGI-I: Patient Global Impression of Improvement Scale.

visits at the department of Physiotherapy- and Occupational Therapy at Copenhagen University Hospital and will be distributed over 16 weeks, with treatment offered in week 0, 2, 5, 8, 12 and 16 (+/−1 week). The physiotherapists delivering the treatments will not be involved in the assessment of outcomes.

2.4.3. Supervised pelvic floor muscle training

In addition to the conservative treatment program, the participants in the PFMT group will receive six individual treatments of 45 min consisting of individually supervised PFMT. The supervised PFMT will be given by one of two physiotherapists specialised in faecal incontinence and pelvic floor disorders. Both of them have over 10 years of experience in treating pelvic floor disorders. At the first visit, the participants receive information about the anatomy and function of the pelvic floor muscles by the use of images and a model of the pelvis. They receive verbal instructions on how to perform a correct pelvic floor muscle contraction and correct contractions will also be taught by digital vaginal and rectal examination. In each session, the participants receive an examination of the function of their pelvic floor muscles by a digital vaginal and rectal examination. The pelvic floor muscles and the external anal sphincter strength will be assessed according to the Modified Oxford Score (ranging 0–5) and endurance of a submaximal contraction will be determined [26]. The function of the pelvic floor muscles will be assessed with intra-anal electromyography (EMG)-biofeedback using the U-control EMG-trainer and an anal probe from Thought Technology Ltd, Canada. This 'strength biofeedback training' will be used to give the participants visual and auditory feedback on a contraction in order to enhance the awareness, strength and endurance of a correct pelvic floor muscle contraction [13,17–19,27]. The biofeedback assessment will be conducted with the participant in a lying position and, from the second visit, with the participant in a lying, sitting and standing position. Static and dynamic endurance will be determined in all positions, as will the ability to perform a pelvic floor muscle contraction before and during coughing, transfers, lifting and walking. According to the findings from the physiotherapeutic examination, a home training program is prepared. The training program will be individually adapted according to the abilities of each participant. Participants will be instructed in submaximal contractions and relaxation of the muscles between contractions. Submaximal contractions are chosen to ensure a correct pelvic floor muscle contraction

where participants are able to breathe freely and avoid activation of muscle synergists like the gluteal, thigh or abdominal muscles. The training program consists of three sets of 10 pelvic floor muscles contractions sustained for up to 10 s and two sets of three contractions sustained for up to 30 s. Participants will be instructed in a 1-min rest between each set and between each of the 30 s contractions. Participants with low muscular endurance will be instructed to hold the contractions according to the findings from the physiotherapeutic examination. For example, a participant with low muscular endurance could be instructed to perform six sets of five contractions sustained for 5 s and then increase the duration and number of the contractions in each set until he/she is able to perform the described program. Participants who experience difficulties in performing a correct pelvic floor muscle contraction will be instructed to check their contraction by palpation at the anus and/or perineum when training at home in order to achieve a correct contraction. The participants will be encouraged to perform the training program at home on a daily basis. They will also be taught to contract the pelvic floor muscles in response to faecal urgency and in situations with increased abdominal pressure. Participants will receive written training materials with explanations and illustrations along with the verbally and digitally provided instructions (See Fig. 2 for the illustrations explaining a correct pelvic floor muscle contraction and Additional file 2 for the training materials).

The participants will be instructed to fill out a training diary (See Additional file 3) which also contains their individual home training program. The training diary is used as a motivational tool and to quantify training adherence. At each follow-up visit, the training diary will be evaluated and any problems will be discussed with the physiotherapist. To achieve overload of the pelvic floor muscles, the training program will be progressed at each follow-up visit based on the findings from the examination. As the participants make progress they will be instructed to perform the exercises in different body positions such as sitting, bending forward and standing and during movements such as transfers, lifting, walking and coughing. For an overview of the content of the physiotherapeutic treatment, see Table 1.

2.4.4. Standardisation of the supervised PFMT

To achieve standardisation of supervised PFMT treatments, a written protocol for the physiotherapeutic examinations and PFMT program will be provided to the physiotherapists delivering the treatments (See Additional file 4). This protocol contains a thorough description of the physiotherapeutic examination and the supervised PFMT to be delivered at each visit with the physiotherapist. The physiotherapists will be instructed in the use of this protocol before trial start and adherence to the protocol will be recorded by the physiotherapists filling in a case report form for each visit. If the physiotherapists should have any clarifying questions about conducting the intervention during the trial, they will be able to contact the primary investigator anytime.

2.4.5. Attention-control massage treatment

The attention control group will receive the same conservative treatment as the PFMT group, but instead of the supervised PFMT, they will receive six treatments of 30 min consisting of massage of the neck and back. The participants in the attention-control group will be given no instructions in PFMT, but, on the other hand, they will not be asked to refrain from performing PFMT on their own. The attention-control massage treatment is chosen to give the participants in the attention-control group the same number of visits and approximately the same amount of attention from the health care professional. Moreover, we consider the massage treatment to represent an inactive control treatment, since it is shown not to improve urinary incontinence [28], a condition that shares many of the known risk factors for faecal incontinence [29].

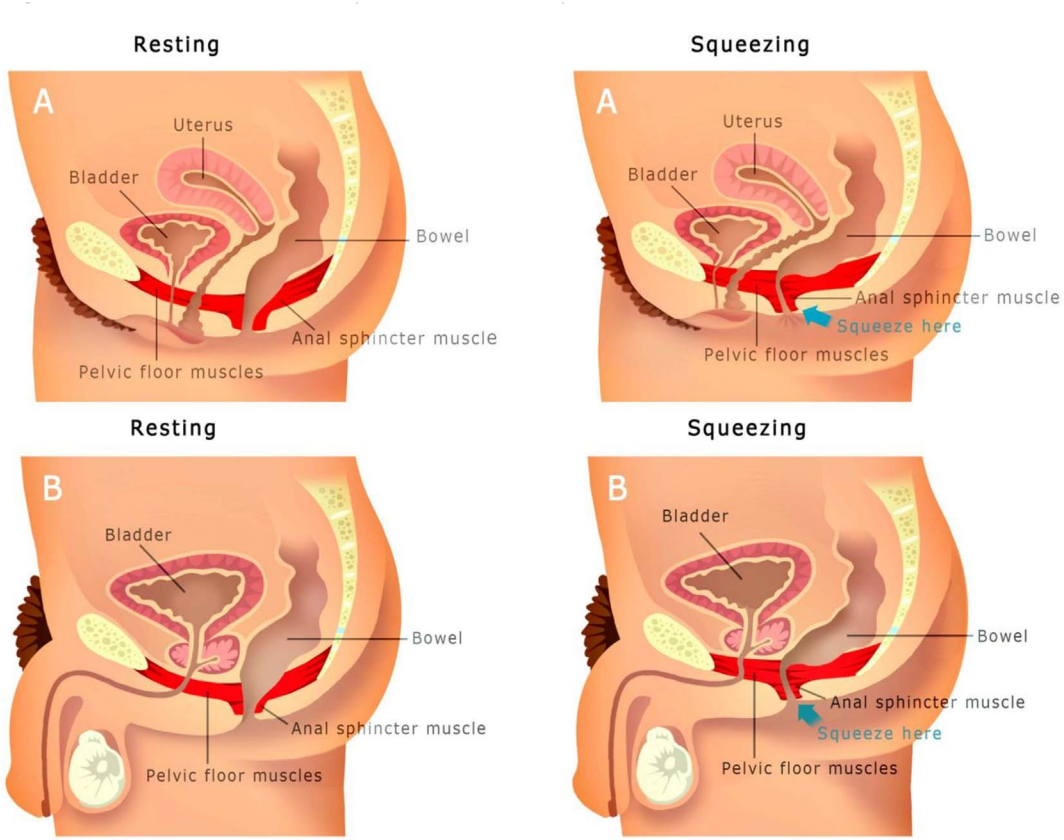

Fig. 2. Illustrations from the written training materials illustrating a correct pelvic floor muscle contraction for a) women and b) men. Copyright: JohannesBojesen.com. For the complete written training materials please see Additional file 2 for the training materials and Additional file 3 for the training diary.

Table 1
Supervised Pelvic floor muscle training (PFMT).

	Training week 0	Training week 2	Training week 5	Training week 8	Training week 12	Training week 16
45 min supervised PFMT	+	+	+	+	+	+
Digital vaginal and rectal examination	+	+	+	+	+	+
Correct contraction taught digitally	+	+	+	+	+	+
Biofeedback in lying position	+	+	+	+	+	+
Biofeedback in sitting and standing position		+	+	+	+	+
Preparation of an individual home training program	+					
Progression of the individual home training program		+	+	+	+	+
Motivational training-dairy review		+	+	+	+	+
Collection of adherence data (training dairy)		+	+	+	+	+

2.5. Blinding

2.5.1. Blinding of participants

Given the nature of the intervention and the attention-control treatment, it is not possible to blind the participants or the physiotherapists delivering the PFMT. All three nurses delivering the conservative treatment will be blinded to the allocation to trial arms. All investigators, health care providers and outcome assessors are thoroughly instructed not to reveal to the participants that we expect the supervised PFMT to be more effective than the attention-control massage treatment. The treatments are presented as equal both in the written and verbal information given at enrolment and at follow-ups. Thus attempts are made to blind the participants to the trial hypothesis [30].

2.5.2. Blinding of researchers and outcome assessors

The primary investigator (AU) enrolling the participants and collecting baseline data (before randomisation) is blinded with respect to group allocation. The research nurse (ID) conducting the anorectal manometry and rectal capacity measurements at baseline (before randomisation) and at the 16-week follow-up remains blinded to group allocation. She is also blinded when handling the 16-week follow-up questionnaires (primary and secondary outcomes at the primary endpoint). The colon and rectal surgeon (MS) conducting the examination and endoanal ultrasound investigation at the 16-week follow-up is also blinded to group allocation. Thus, all outcome assessors are blinded with respect to group allocation. All data will be entered blinded and validated using double entry.

2.6. Baseline data

After the participants have signed the informed consent form, the primary investigator (AU) will collect the baseline data and distribute a 14-day bowel diary. Baseline data consists of: demographic background information, a medical history with emphasis on the history of faecal incontinence and known risk factors for faecal incontinence and for the women an obstetric history. The participants fill out validated questionnaires measuring severity of faecal incontinence and condition-specific quality of life: The Fecal Incontinence Severity Index (FISI), the Vaizey Incontinence Score and the Fecal Incontinence Quality of Life Scale (FIQL) (See Outcome measures below). If the participants should have any clarifying questions in relation to filling out the questionnaires, they are allowed to ask the primary investigator. After 2–4 weeks, the participants return to the Department of Surgical and Medical Gastroenterology. A research nurse blinded to group allocation collects the 14-day bowel dairy and conducts an anorectal manometry and rectal capacity measurements. The participants then go to a secretary in the Department of Physiotherapy- and Occupational Therapy who will perform the randomisation of the participants.(For trial flow, see Fig. 1).

2.7. Outcome measures

Outcome measures will be assessed at baseline before randomisation, within 14 days after completion of the 16-week PFMT treatment or attention-control massage treatments (primary endpoint) and at follow-up 36 months after completing the treatments (still ongoing) using both patient-reported outcomes and objective outcomes. The participants will complete self-reported questionnaires and a 14-day bowel diary. Also, anorectal manometry, rectal capacity measurements and an endoanal ultrasound will be conducted. For a schedule of the outcome measures, see Table 2, and for participant timeline, including a schedule of visits, events and data collection, see Table 3.

2.7.1. Primary outcome

The Patient Global Impression of Improvement Scale (PGI-I) [31] is used as the primary efficacy outcome measure. The scale is validated to measure subjective treatment effect in relation to urinary incontinence [31] and pelvic organ prolapse [32]. The scale is a self-rated assessment of changes in incontinence symptoms after treatment. The participants are asked to compare their faecal incontinence symptoms before and after the 16 weeks of treatment and to rate the degree of changes in their symptoms. On a seven-point Likert scale, they indicate if their incontinence symptoms after the 16 weeks of treatment are: very much better, much better, a little better, unchanged, a little worse, much worse or very much worse compared to the period prior to the trial [31]. This scale is chosen since faecal incontinence is a symptom primarily affecting quality of life. On this basis, it is argued that treatment efficacy in people with faecal incontinence is best measured by the person's subjective impression of symptoms (e.g. PGI-I) and by measures of condition-specific quality of life [33,34].

Table 2
Data collection/outcome measures.

Variable	First baseline visit	Second baseline visit	16-week follow-up	36-month follow-up
Demographic data	+			
Medical history	+			
Obstetric history	+			
Incontinence history	+			
PGI-I (primary outcome)			+	+
Vaizey Incontinence Score	+		+	+
FISI	+		+	+
FIQL	+		+	+
14 days bowel dairy	+		+	
Anorectal manometry		+	+	
Rectal capacity measurements		+	+	
Endoanal ultrasound			+	

Abbreviations: FISI: Fecal Incontinence Severity Index, FIQL: Fecal Incontinence Quality of Life Scale: PGI-I: Patient Global Impression of Improvement Scale.

Table 3
Participant timeline.

	Study period							
	Pre-allocation/enrolment				Allocation	Post-allocation		
Time point	Screening visit	Information visit	First baseline visit	Second baseline visit	Allocation	Treatments in week 0, 2, 5, 8, 12 and 16	16-week follow-up (Primary endpoint)	36-month follow-up
Enrolment:								
Eligibility screening	+	+						
Verbal and written information	+	+						
Informed consent		+						
Allocation					+			
Interventions:								
PFMT						+		
Attention-control massage treatment						+		
Assessments:								
Baseline variables								
Demographic data			+					
Medical history			+					
Obstetric history			+					
Incontinence history			+					
Outcome variables								
Self-reported questionnaires								
PGI-I (Primary outcome)							+	+
Vaizey Incontinence Score			+				+	+
FISI			+				+	+
FIQL			+				+	+
14-day bowel diary			+				+	
Physiological measurements								
Anorectal manometry				+			+	
Rectal capacity measurements				+			+	
Endoanal ultrasound							+	
Adherence:								
Adherence to PFMT-intervention (Training diary)						+		

Abbreviations: FISI: Fecal Incontinence Severity Index, FIQL: Fecal Incontinence Quality of Life Scale, PFMT: Pelvic floor muscle training, PGI-I: Patient Global Impression of Improvement Scale.

2.7.2. Secondary outcomes

2.7.2.1. The following outcome measures are the secondary outcomes. Vaizey Incontinence Score: This is a validated summary scale measuring severity of faecal incontinence, ranging from 0 – 24, 0 = complete continence, 24 = complete incontinence [35]. The scale distinguishes between incontinence for flatus, thin and formed stool. Participants rate the frequency of each incontinence item in five categories with frequencies ranging from less than once monthly to daily. The presence of faecal urgency, use of pads and medication and changes in life style in relation to faecal incontinence is also registered [35].

Fecal Incontinence Severity Index (FISI): FISI is a validated severity scale for faecal incontinence ranging from 0 – 61, 0 = complete continence, 61 = complete incontinence [36]. The scale distinguishes between incontinence for gas, mucus, liquid and solid stool. Participants rate the frequency of each incontinence item in six categories. Frequencies range from one to three times per month to two or more times per day. Values for all categories are summed. The values are weighted and reflect patients' subjective impression of severity. In this trial, the patient-weighted scores are used [36].

Fecal Incontinence Quality of Life Scale (FIQL): FIQL is a validated condition-specific quality of life Scale [33,37]. The Scale consists of 29 questions divided into four sub-scales: Lifestyle, Coping/behaviour, Depression/self-perception and Embarrassment [37]. Items are generally scored on a four-point Likert scale ranging from ‘most of the time’ to ‘none of the time’ or from ‘strongly agree’ to ‘strongly disagree’. The values in each subscale are summed and divided by the number of items in the subscale. Each subscale range from 1 – 4, 1 = worst quality of life, 4 = best quality of life.

All four of the PGI-I, the Vaizey Incontinence Score, the FISI and the FIQL are validated in their original language, but have not been comprehensively validated for a Danish population. In this trial, we use the Danish versions of the questionnaires that are generally used in Denmark, which have only been linguistically validated.

Bowel diary: The participants fill out a paper bowel dairy for 14 days where they report the number of stools, episodes of faecal urgency, soiling and incontinence as well as the use of pads and laxatives. Limitations in daily life due to faecal incontinence are also reported. The participants are instructed to fill out the diary at the end of the day or to use real time assessment during the day by their own choice [38].

Anorectal manometry and rectal capacity measurements: A specialised nurse (ID) will conduct anorectal manometry and rectal capacity measurements. She has over 10 years of experience in conducting these investigations. All measurements are recorded with the physiologic recorder Polygraf ID from Medtronic, Denmark using the Polygram NET software, Medtronic, Denmark. Anorectal manometry is performed to measure anal sphincter pressures to get an objective evaluation of the function of the pelvic floor muscles and rectum capacity. By this, objective changes after the treatments can be documented [39,40]. The investigation is conducted by the water perfused catheter technique using a single-use anorectal 8ch catheter from Sandhill, USA. With the participant lying in the left lateral position and hip flexed to 90°, a

balloon catheter is inserted into the rectum. Resting pressure and maximum squeeze increment pressure is determined. Both measures are recorded in the high pressure zone using the pull through technique [39]. Rectal capacity measurements of the rectum are performed by the use of a single-use 4ch catheter from Sandhill, USA. The catheter is inserted into the rectum and then slowly inflated with air. Sensory threshold is determined as the minimum volume of filling where a rectal sensation is perceived. Urge sensation is determined as the volume associated with the initial urge to defecate and maximum tolerated volume is determined as the volume where the participants feel a strong desire to defecate and feel pain or discomfort.

3D Endoanal ultrasound and gynaecological and rectal examination: An experienced colon and rectal surgeon (MS) conducts a gynaecological and rectal examination. To detect internal and/or external anal sphincter defects, the examination is supplemented by endoanal ultrasonography. The investigation is conducted with the ultrasound system Flex Focus 500 from BK Medical, Denmark using the anorectal 3D transducer 2052, 13 MHz from BK Medical, Denmark. The system provides a three-dimensional image of the sphincter complex and the puborectal muscle. With the participant lying in the supine position, the probe is inserted into the anal canal just above the level of the puborectal muscle. The different components of the anal sphincter complex and the puborectal muscle are visualised and a 360-degree image is created. Sphincter defects in the internal and/or external sphincter are defined as a gap in the muscle ring or a loss of muscle substance in a range of more than 60°. The extension of sphincter defect is measured in degrees.

2.7.3. Minimizing missing data

To minimise missing data for the primary endpoint, all participants will be reminded about the 16-week assessment visit (primary endpoint) by a telephone call from the primary investigator 14 days before the visit. At the same time, the participants will be encouraged to begin filling out the bowel diary.

2.7.4. Deviations from the trial protocol and trial registration

Initially, a 12-month follow-up was planned and described in the trial registry. For logistical reasons, however, we failed to perform the 12-month follow-up for the first 15 participants. Because of this, we decided to change the 12-month follow-up to 36 months. This will enable us to perform a long-term outcome assessment for all included participants. This change does not affect the pre-specified primary endpoint, that is, the participants' rating of changes in their incontinence symptoms after 16 weeks of treatment measured by the PGI-I. To achieve as high response rate as possible, we decided to restrict the 36-month follow-up measurement to the PGI-I, the Vaizey Incontinence Score, the FISI and the FIQL. Additional questions about further treatment for faecal incontinence since completion of the trial will be added to the 36-months follow-up assessment, as will questions about the current amount of PFMT. The follow-up questionnaire will be handled by post. Reminders will be sent to non-responders after 4 weeks, and followed up with telephone calls.

Originally, it was planned to measure maximum squeeze duration as a part of the anorectal manometry investigation. Maximum squeeze duration is defined as the time the participants could hold a squeeze from maximum increment squeeze pressure to a drop of 50% of maximum increment squeeze pressure. The maximum squeeze duration was measured three times with a stationary probe for up to a maximum of 30 s. The participants had 1 min's rest between each of the three trials. It was planned to determine maximum squeeze duration as the average of these three trials. As a part of the ongoing data quality check during the data collection it became clear that it was difficult to determine the time duration of a maximum squeeze with the stationary probe. Therefore, it was decided to not use the data for maximum squeeze duration in further analysis.

2.8. Sample size

The sample size is calculated in relation to the PGI-I (primary outcome). Based on previous findings in the literature, we hypothesise that 30% of the participants in the attention-control group [41–43] and 60% of the participants in the PFMT group [13,19,44] will achieve improvement in relation to their faecal incontinence symptoms. Improvement is defined as participants reporting 'very much better', 'much better' or 'a little better' using the PGI-I. Based on a binomial distribution, we will need a sample size of 84 to show this clinically relevant difference in treatment effect between groups using a statistical power of 80% and a significance level of 5% (two-tailed). To account for a dropout rate of 16%, we aim to include 100 participants.

2.9. Data management

The data will be handled in accordance with the rules from the Danish Data Protection Agency. All data will be collected on paper case report forms that will contain no information on group allocation. An exception to this will be data from the training diaries and case report forms from the supervised PFMT-treatments, as this data will inherently only exists for the PFMT-group and will be stored separately. After collection, all case report forms will be checked for data quality and missing values and will be stored in a locked cabinet to which only the primary investigator has access. All data will be double-entered in EpiData Entry version 3.1, Epidata Associations, Odense, Denmark. A standard coding manual describing data entry is developed to reduce errors and ensure comprehension under the analyses. Data entry will be validated by checks for valid values and range checks. For the analyses, the data will be exported to SAS Enterprise Guide 7.1, SAS institute Inc., Cary, NC, USA. The electronic database and analyses will be stored on a secure computer server with personal log-in access authorised by the primary investigator. The primary investigator will have access to the full data set (blinded to group allocation) and co-investigators will be given access when needed. After completion of the trial, all data and trial documents will be archived by the primary investigator and stored for 5 years at the Department of Physio- and Occupational Therapy at Hvidovre University Hospital.

2.10. Statistical analysis plan

2.10.1. Recruitment and withdrawals

Recruitment rates and numbers of withdrawals and dropouts will be reported along with reasons for exclusions, dropouts and withdrawals.

2.10.2. Baseline data

Baseline data will be presented as medians (with range) for continuous data. Categorical variables will be presented as frequencies and percentages.

2.10.3. Session attendance and adherence

Session attendance in both groups will be presented as median number of consultations (with range) with the physiotherapist. Adherence to the pelvic floor muscle home training program will be presented as median number of days (with range) and the corresponding percentage, where the participants have noted training in the diary. Adherence will also be calculated as the percentage of participants who have attended at least four of six consultations with the physiotherapist, and at the same time have trained on at least 70% of the possible 112 training days corresponding to approximately 5 training days per week on average. We consider this as a minimum exposure for the per-protocol analysis.

2.10.4. Primary analysis of the primary outcome

The purpose of the primary analysis is to test the trial hypothesis that supervised PFMT in combination with conservative treatment is

superior to attention-control treatment and conservative treatment alone in the treatment of faecal incontinence. The data for the primary outcome, the participants' ratings of changes in their incontinence symptoms at PGI-I after 16 weeks of treatment, will be analysed in order to compare differences in treatment effects between the two groups.

Estimates of treatment effect for the primary outcome will be calculated using an 'intention to treat' analysis, including all randomised participants regardless of adherence to the intervention and dropouts. To create a full analysis data set, missing data for the primary outcome will be imputed with a score of 'unchanged' in both groups. The primary analysis will be carried out using logistic regression with PGI-I scores as the dependent variable. The PGI-I outcomes will be dichotomised into symptoms improvement (PGI-I scores of 'very much better', 'much better' or a 'little better') or unchanged/worsening symptoms (PGI-I scores of 'unchanged', 'a little worse', 'much worse' or 'very much worse'). By this we can calculate the odds ratio for participants in the PFMT-group reporting improvement of their incontinence condition after 16 weeks of treatment corresponding to the three upper values at the PGI-I (very much better, much better, a little better). The attention-control group will be the reference group.

The estimates of the size of treatment effect will be presented along with 95% confidence intervals and actual p-values. Levels of significance will be set at 0.05. The independent variable will be group allocation. The primary analysis will be unadjusted.

2.10.5. Secondary analysis of the primary outcome

We will report the absolute numbers and proportions of participants in each group stating each of the seven categories at the PGI-I: very much better, much better, a little better, unchanged, a little worse, much worse or very much worse and the prevalence of participants reporting either improvement in their incontinence condition (a PGI-I score of 'very much better', 'much better' or a 'little better') or unchanged/worsening symptoms (a PGI-I score of 'unchanged', 'a little worse', 'much worse' or 'very much worse').

Also a proportional odds model will be fitted with the PGI-I scores as outcome including all seven categories. In case the proportional odds assumption is not fulfilled a multinomial logit model will be fitted comparing the PFMT group and the attention-control group. In the case that a multinomial logit model is necessary, then if there is fewer than 10 observations in one category this category will be grouped together to the category next to in the less extreme direction.

Sensitivity analyses for the primary outcome will be made if missing values appear to depend on group allocation or if over 10% of the participants have missing values for the primary outcome. In these cases, the primary analysis will be supplemented by sensitivity analyses using worst case and best case scenarios. In the worst case scenario, missing values for the attention-control group will be imputed with a score of 'very much better'. If no participants (in either group) have scored 'very much better' we will impute the most extreme positive value observed. For the PFMT group missing, values will be imputed with a score of 'very much worse' or if no participants have scored 'very much worse', with the most extreme negative value observed. In contrast, in the best case scenario, missing values will be imputed, with a score of 'very much worse' for the attention-control group and a score of 'very much better' for the PFMT group or the most extreme values observed.

In order to examine the influence of potential confounders and modifiers, multiple analyses will be conducted. The modifiers that will be taken into account are significant baseline differences, use of anti-diarrhoeal medication and use of fibre supplements at baseline, detected anal sphincter injuries at endoanal ultrasound, stool consistency, incontinence type (urgency, passive or both) and the presence of urinary incontinence. The modifiers will be modelled by adding interaction terms to the multiple analyses. In cases of statistical interaction, the effect of the intervention will be reported in strata representing each level of the modifying variable along with the main effect of the treatment groups.

To account for differences in adherence to the PFMT intervention, a per-protocol logistic regression analysis will be undertaken following the principles outlined above. This per protocol analysis will include participants who have attended at least four of six consultations with the physiotherapist, and who at the same time, have documented training on at least 70% of the possible training days corresponding to approximately 5 training days per week on average.

2.10.6. Analyses of secondary outcomes

Analyses of secondary outcomes supporting the primary outcome: The secondary outcome measuring condition-specific quality of life, the FIQL,-and the two secondary outcomes measuring faecal incontinence severity, the FISI and the Vaizey Incontinence Score, are considered supportive for the primary analysis of the primary outcome. All other secondary analyses are considered explorative secondary analyses. The three supportive outcome measures will be analysed using multiple linear regression analyses with group allocation as the independent variable. Investigation of confounders and modifiers will be conducted the same way as for the primary analysis. Changes from baseline to end of treatment (after 16 weeks) will be reported as estimates of mean difference in treatment effect between groups. For the FIQL, the mean differences in change between groups will be reported within the four subscales: Lifestyle, Coping/behaviour, Depression/self-perception and Embarrassment. The analyses for the three supportive outcomes will be conducted both according to the intention to treat principle and as per-protocol analyses as outlined above. Missing data will be handled by multiple imputation.

Explorative analyses of the secondary outcomes: Data from the anorectal manometry investigations, rectal capacity measurements and continuous data from the bowel diary (number of stools and incontinence episodes) will be conducted as per protocol analyses using multiple linear regression analyses with group allocation as the independent variable. Results will be reported as mean differences between groups from baseline to end of treatment (after 16 weeks). Missing data will be handled by multiple imputation. As paper diaries are prone to low compliance and missing data [42,45], we will conduct a sensitivity analysis in case of missing data exceeds 10% for the bowel diaries or the missing data appear not to be missing at random. In this analysis, missing values will be imputed using multiple imputation for variables where missing values are jugded to be missing at random (no specific pattern in the missing data). But at the same time, for variables where missing values are judged not to be missing at random (data are generally missing for a specific items unless that specific item is scored positively) missing values will be replaced with a score of zero for numeric questions and a negative answer for yes/no questions.

All estimates of treatment effect will be presented as mean differences in change between groups with 95% confidence intervals. All regression models will be controlled for goodness-of-fit by evaluation of whether the data meet the assumptions of linearity, normal distribution and variance homogeneity. Normal distribution of the residuals will be checked by visual inspection of residual plots, scatterplots and histograms. Remodelling will be performed when appropriate.

Statistical analyses will be performed using SAS Enterprise Guide 7.1 SAS institute Inc., Cary, NC, USA. All analyses will be conducted by researchers blinded for group allocation. For all statistical tests the actual two-sided p-value will be reported, values below 0.05 will be considered statistically significant.

2.10.7. Analyses for the secondary endpoint at the 36-month follow-up

Analyses of the PGI-I, the Vaizey Incontinence Score, the FISI and the FIQL at the 36-month follow-up will be conducted in the same way as for the primary endpoint as described above.

2.11. Data monitoring

It is decided to not set up a data monitoring committee for the trial because both the supervised PFMT and the attention-control treatment are regarded as safe interventions [18,46]. No interim analysis or stopping guidelines will be applied to the trial. All physiotherapists and outcome assessors are instructed to report any adverse events during the trial to the primary investigator via weekly conferences that allow discussion of the conduct of the trial and any adverse events. All adverse events will be reported annually to the Health Research Ethics Committee and all serious adverse events will be reported immediately. Since the trial is not investigating clinical products or drugs, the trial is not covered by the Good Clinical Practice regulations. Therefore, no regulatory auditing of the trial is prescribed by law. The trial can be subject to unannounced audits by the local regional Health Research Ethics Committee or Danish Data Protection Agency.

3. Discussion

This trial will show whether supervised PFMT in combination with conservative treatment is superior to attention-control massage treatment and conservative treatment in patients with faecal incontinence. This will be based on changes in faecal incontinence symptoms after 16 weeks of treatment using the PGI-I. The efficacy of PFMT and biofeedback training for faecal incontinence is unclear. Previous trials have lacked an attention-control group in the form of a non-training comparator. This trial adds an attention-control group receiving the same number of visits and approximately the same amount of attention as the PFMT group. We consider the attention-control massage treatment to represent an inactive control treatment, since it has been shown not to improve urinary incontinence [28] which shares many of the known risk factors for faecal incontinence. Adding this attention-control group will enable us to evaluate the true efficacy of supervised PFMT controlled for the placebo effect associated with attention given by the healthcare professional. This knowledge will help to clarify the role of pelvic floor muscle training for faecal incontinence and permit evidence-based recommendations about PFMT as a part of the first-line treatment for faecal incontinence.

In this trial, we have chosen the individualised, supervised approach to PFMT, including palpation of a correct contraction. This is because, it is shown that up to 40% of women with pelvic floor disorders fail to achieve a correct pelvic floor muscle contraction after written or verbal instructions alone [47,48]. This fact, along with individualised progression of the PFMT, can be challenging in a group setting.

It can be difficult to blind participants and health care providers when examining a physiotherapeutic intervention. In this trial, instead we seek to blind the participants to the trial hypothesis. The participants are thus not informed, neither verbally nor in writing, that we expect the supervised PFMT to be more efficient than the attention-control massage treatment. It is decided not to ask the attention-control group to refrain from performing PFMT on their own. Attempts to restrict the attention-control group from performing PFMT can reveal the study hypothesis and at the same time it is not possible to control whether the participants in the attention-control group actually refrain from performing PFMT.

The optimal patient-reported outcome for evaluating treatment efficacy for faecal incontinence is debated [49]. In this trial, the PGI-I is chosen as the primary outcome. This is because it is recommended to measure treatment efficacy by eliciting the person's subjective impression of symptoms after treatment [33,34]. Other trials have used the Vaizey Incontinence Score as their primary outcome. We decided not to do so because the Vaizey Incontinence Score is shown to contain items insensitive to treatment effect [50] and has been criticised for mixing measurement of severity, social impact and coping strategies [33,49].

In the absence of an optimal patient-reported outcome for measuring faecal incontinence, we decided to include the three secondary patient-reported outcomes: the Vaizey Incontinence Score, the FISI and the FIQL, all of which we consider to be supportive of the primary outcome. This is in line with the recommendations of including both severity measures, subjective rating of improvements and condition-specific quality of life measures when evaluating treatment efficacy in faecal incontinence [33,49]. It is a weakness that the Danish versions of the PGI-I, the Vaizey Incontinence Score, the FISI and the FIQL used in this trial are not comprehensively validated in a Danish population, but only linguistically validated. The questionnaires are all comprehensively validated in their original language. It is unfortunately beyond the scope of this trial to validate the Danish language versions of these patient-reported outcomes before conducting the trial. Instead, we use the Danish versions that are generally used in Denmark.

Trial status

To date, we have enrolled 102 participants in the trial and have completed the baseline and 16-week assessment (primary endpoint). Hence, trial recruitment has stopped, but data collection for the 36-month outcome assessment will continue until June 2019. The data are currently being cleaned and double-entered (no data lock), no analyses have been made, and the treatment group allocation remains blinded.

Ethics

The trial is approved by the Health Research Ethics Committee of the Capital Region of Denmark (Protocol number H-2-2012-067), the Danish Data Protection Agency (Identification number HVH-2012-031) and pre-registered at ClinicalTrials.gov (Identification number NCT01705535). Protocol amendments will be submitted to the respective institutions. Informed consents are obtained in accordance with the Declaration of Helsinki. Before signing the consent forms, participants are informed that participation in the trial is voluntary and that the decision of participating would not affect their rights for treatment. They are also informed that they can withdraw anytime without affecting their rights for further treatment. After the completion of the 16 weeks of treatment and collection of the primary and secondary outcomes at the 16-week follow-up, participants in the attention-control group will be offered a supervised PFMT-program identical to the intervention treatment. After the primary endpoint at the 16-week follow-up, participants from both the attention-control group and the PFMT-group will be offered further treatment for faecal incontinence if necessary.

Consent for publication

Not applicable.

Availability of data and material

Access to the anonymised data at individual level will be made public when publishing the results.

Competing interest

MS is protector for Medtronic and has received a speaker's fee and teaching fee from Medtronic and funding of projects from the Medtronic company and from Helsefonden (a public national foundation funding social and health-related topics).

UD is a board member of the Danish Society of Physiotherapy (an umbrella Society for Danish Physiotherapy Societies) and chairwoman for The Danish Society of Urological, Gynaecological and Obstetrical Physiotherapy. UD is also a board member of the Danish Continence Society (a non-profit patient organisation). UD has been paid as a

consultant for Astellas Pharma, a company that produces medication for overactive bladder, and as a consultant for Coloplast and for SCA—Svenska Cellulosa Aktiebolaget, companies that produce personal care products related to incontinence. UD has no financial relations with any of the companies other than payment for consultancy. All other authors declare that they have no competing interests.

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Authors' contributions

AU designed the trial in collaboration with UD, MS, ID and TB. AU is the primary investigator and project leader. AU, TB and JP designed and drafted the statistical analysis plan. The first draft of this manuscript was written by AU and TB, after which all authors critically revised the manuscript. All authors read and approved the final version of the manuscript before submitting it for publication. AU and TB are responsible for the completion of the trial and communicating the trial results.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2017.07.006.

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