BMJ Open

The efficacy of Periacetabular osteotomy followed by progressive resistance training versus progressive resistance training as non-surgical treatment in patients with Hip dysplasia (PreserveHip). A randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032782
Article Type:	Protocol
Date Submitted by the Author:	05-Jul-2019
Complete List of Authors:	Reimer, Lisa; Aarhus University Hospital, Orthopedic Surgery Jakobsen, Stig; Aarhus University Hospital, Orthopedic Surgery Mortensen, Louise; Aarhus University Hospital, Orthopedic Surgery Dalgas, Ulrik; Aarhus University, Public Health - Sport Jacobsen, Julie; VIA University College, Physiotherapy & Research Centre in Health and Welfare Technology Soballe, Kjeld; Aarhus University Hospital, Orthopedic Surgery Bere, Tone; Oslo University Hospital, Orthopedic Surgery Madsen, Jan; Oslo University Hospital, Orthopedic Surgery Nordsletten, Lars; Oslo University Hospital, Orthopedic Surgery; University of Oslo, Faculty of Medicine Risberg, May Arna; Oslo University Hospital, Orthopedic Surgery Mechlenburg, Inger; Aarhus University Hospital, Orthopedic Surgery; Aarhus University, Clinical Medicine
Keywords:	Hip < ORTHOPAEDIC & TRAUMA SURGERY, Hip dysplasia, Periacetabular Osteotomy, PAO, Progressive Resistance Training, Osteoarthritis

Protocol article version 4. 12.07.19

The efficacy of Periacetabular osteotomy followed by progressive resistance training versus progressive resistance training as non-surgical treatment in patients with Hip dysplasia (PreserveHip). A randomised controlled trial.

Researchers and institutions
Lisa Cecilie Urup Reimer[a], MSc, lisareimer@clin.au.dk
Stig Storgaard Jakobsen[a], PhD, stig.jakobsen@clin.au.dk
Louise Mortensen[a], MSc, lpmortensen@hotmail.com
Ulrik Dalgas[b], PhD, dalgas@ph.au.dk
Julie Sandell Jacobsen[c], MSc, jsaj@via.dk
Kjeld Søballe[a], DMSc, kjeld@soballe.com
Tone Bere[d], PhD, bereto@ous-hf.no
Jan Erik Madsen[d], PhD, j.e.madsen@medisin.uio.no
Lars Nordsletten[de], PhD, lars.nordsletten@medisin.uio.no
May Arna Risberg[d], PhD, m.a.risberg@nih.no
Inger Mechlenburg[af], PhD, DMSc, inger.mechlenburg@clin.au.dk

[a]Department of Orthopedic Surgery, Aarhus University Hospital, Denmark.
[b]Department of Public Health – Sport, Aarhus University, Denmark
[c]Department of Physiotherapy & Research Centre in Health and Welfare Technology, VIA University College, Aarhus, Denmark
[d]Department of Orthopedic Surgery, Oslo University Hospital, Norway
[e]Faculty of Medicine, University of Oslo, Norway
[f]Department of Clinical Medicine, Aarhus University, Denmark

Corresponding author
Name: Lisa Cecilie Urup Reimer
Adress: Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
E-mail: lisareimer@clin.au.dk
Phone: +45 26 47 40 80

Word count
3.383 words

Protocol article version 4. 12.07.19

ABSTRACT

Introduction

Periacetabular osteotomy (PAO) is an established treatment for adolescent and adult patients with hip dysplasia. However, the efficacy of PAO has not been tested against another surgical intervention or conservative treatment in a randomised controlled trial before. We suggest that progressive resistance training (PRT) could be an alternative to PAO. The primary aim of this trial is therefore to examine the efficacy of PAO followed by 4 months of usual care followed by 8 months of PRT compared to 12 months of solely PRT in patients with hip dysplasia eligible for PAO in terms of patient-reported pain measured by The Copenhagen Hip and Groin Outcome Score (HAGOS).

Methods and analysis

This trial is a single blinded multicentre randomised controlled clinical trial, where patients with hip dysplasia, who are eligible for PAO, will be randomised to either PAO followed by usual care and PRT or PRT only. Primary outcome is patient-reported pain, measured on the subscale pain on the Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire 12 months after initiation of PAO or PRT. The key secondary outcomes are the other subscales of the HAGOS, adverse and serious adverse events, usage of painkillers (yes/no) and type of analgesics. Based on the sample size calculation, the trial needs to include 96 patients.

Ethics and dissemination

The trial is approved by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-234-18) and by the Danish Data Protection Agency (Journal No 1-16-02-120-19). The trial is also approved by The Regional Committee for Medical and Health Research Ethics, Region South-East Norway (Ref. 2018/1603). All results from this trial will be published in international peer-reviewed scientific journals regardless of whether the results are positive, negative or inconclusive.

Trial registration

The trial is registered at Clinical Trial (NCT03941171).

Keywords

Hip dysplasia, Periacetabular Osteotomy, PAO, Progressive Resistance Training, Osteoarthritis

Protocol article version 4. 12.07.19

ARTICLE SUMMARY

Strengths and limitations of this trial

- This is the first head-to-head comparison to evaluate the additive effect of PAO in addition to non-surgical treatment in patients with hip dysplasia scheduled for PAO.
- The trial will provide valuable evidence to surgeons, physiotherapists, and decision makers by highlighting the efficacy, benefits and harms of the surgical and non-surgical treatment approach, respectively.
- The results are expected to have an immediate substantial impact on clinical practise by providing new evidence to achieve optimal allocation of health care resources as well as markedly improved knowledge when informing patients with hip dysplasia about their options.
- The trial is a multicentre randomised controlled and assessor blinded trial, conducted at two sites in two countries.
- A limitation is that the patients cannot be blinded towards the intervention.

INTRODUCTION

Hip dysplasia is associated with development of early osteoarthritis (OA) (1–3). However, not everyone with radiologically verified hip dysplasia develops OA. Periacetabular osteotomy (PAO) (4,5) is an established treatment for hip dysplasia in adolescents and adults (6–9). The aim of PAO is to improve pain and prevent secondary OA by improvement the hip biomechanics (10). Given that patients with hip dysplasia are preferably operated before OA progresses, we will never know whether these patients would have developed OA. Of note, a longitudinal trial comparing 136 controls with 81 persons with mild or moderate radiological verified hip dysplasia followed for a decade, did not document a tendency for radiological hip degeneration (11).

Patients with hip dysplasia typically experience hip pain and reduced walking distance. The pain is localised to the groin area and can be sharp, sudden and sometimes radiate towards the knee (12). This results in reduced patient-reported performance-based physical function (7,8,13–15). In addition, Sørensen et al. showed that patients with hip dysplasia had weaker hip flexor and abductor muscles than age and gender matched controls (13). Only few trials have investigated physical training for this patient group (16–18). Importantly, trials in hip OA (19,20) have shown, that progressive resistance training (PRT) seems to be a promising exercise modality that may relieve pain and improve function. To our knowledge, however no trials have applied PRT in hip dysplasia. We therefore performed a pilot PRT trial (14) on 17 patients with hip dysplasia scheduled for PAO and found that PRT is feasible with few and minor adverse events and that the patients were motivated for the training (high training compliance). The pilot trial further indicated decreased patient-reported pain, symptoms and better patient-reported scores for sport and recreation measured by The Copenhagen Hip and Groin Outcome Score (HAGOS). Moreover, we found increased performance-based function and increased hip flexion muscle strength on the affected side. As such, a well-powered RCT comparing PRT to PAO in hip dysplasia seems justified.

In further support of the afore mentioned RCT, patients, their relatives, health care providers and decision makers have a common interest in investigating the efficacy of PAO. As described by Wartolowska et al. (21) it is reasonable to assume that surgery is associated with a placebo effect. Firstly, because invasive procedures have a stronger placebo effect than non-surgical ones and, secondly, because a confident diagnosis and a decisive approach to treatment, typical for surgery, usually results in a strong placebo effect (21). A recent survey (22) among British shoulder surgeons showed that surgeons generally agreed that a placebo component to surgical intervention might exist. With the increased use of PAO worldwide and expanded indications for PAO, such as acetabular retroversion and femoroacetabular impingement syndrome (15,23,24), it is problematic that the efficacy of PAO has not been investigated in a randomised controlled trial.

Aim and hypothesis of the trial

The primary aim of this trial is to examine the efficacy of PAO followed by 4 months of usual care followed by 8 months of PRT compared to 12 months of a PRT only, in patients with hip dysplasia eligible for PAO, in terms of patient-reported pain measured by HAGOS. Secondary aims are to investigate changes in patient-reported symptoms, physical function in daily living, physical function in sport and recreation, hip and/or groin-related quality of life, generic health status, performance-based function, hip muscle strength, physical activity and adverse events between PAO followed by usual care and PRT compared to PRT only. We hypothesise that PAO followed by usual care and PRT results in significantly less pain at 12 months follow-up compared to PRT only.

MATERIAL

Design

This trial is a multicentre randomised controlled and assessor blinded trial, following the CONSORT guidelines (25). Change in primary outcome will be measured from baseline to 12-months follow-up, while change in secondary outcomes will be measured from baseline to 4 and 12-months follow-up. In addition, 5-year and 10-year follow-up with questionnaires is planned.

Patients

Setting and location: Patients will be recruited from the Departments of Orthopaedic Surgery at Aarhus University Hospital, Denmark and at Division of Orthopaedic Surgery at Oslo University Hospital, Norway. Approximately 130 PAOs are performed yearly in Aarhus, and 40 PAO are performed in Oslo yearly. We expect to recruit 96 patients. Both centers will be including patients, but the analysis will be performed at Aarhus University Hospital.

Eligibility criteria:

1. Patients aged 18-40 years and diagnosed with hip dysplasia referred from primary care to the Department of Orthopaedic Surgery at one of the two participating hospitals.

2. Considered eligible for PAO by a surgeon.
3. Radiographically verified hip dysplasia (CE-angle <25 degrees and AI-angle >10 degrees) and clinical symptoms.
4. Range of motion: internal rotation >15 degrees, external rotation >15 degrees, hip flexion >110 degrees.
5. Able to drive or commute to training sessions.

Exclusion criteria:

1. OA degree >1 on classification of Tönnis.
2. CE-angle <10 degrees.
3. Retroverted acetabulum (cross over sign and posterior wall sign).
4. Previous pelvic surgery for hip dysplasia (affected side).
5. Calvé Legg Perthes or epifysiolysis.
6. Simultaneous bilateral PAO.
7. Previous surgery for herniated disc, spondylodesis, arthroplasty of hip, knee or ankle.
8. Previous surgery of the hip (tenotomy of iliopsoas tendon, z-plastic of the iliotibial tract or hip arthroscopy) in index leg.
9. Neurological or rheumatoid diseases that affect the hip function.
10. Inadequacy in written and spoken Danish or Norwegian.
11. Body Mass Index (BMI) >25.

Randomisation

After baseline assessment, the patients will be randomised in a 1:1 ratio to either PAO followed by usual care and PRT (PAO-group) or PRT only (PRT-group). A computer-generated list of random numbers will be set up in the Research Electronic Data Capture (REDCap) randomise tool. Administrators of the randomisation procedure will be blinded to block sizes and randomisation sequence at all times during the trial period. Allocation concealment will be ensured, as the randomisation will not be performed and revealed before the patient has been irreversibly included in the trial. After randomisation a secretary or project coordinator, who is otherwise not affiliated with the trial, will refer patients to surgery or to the treating physiotherapist/physiotherapy student who contacts the patient for an appointment of the first exercise session.

PRT-group:

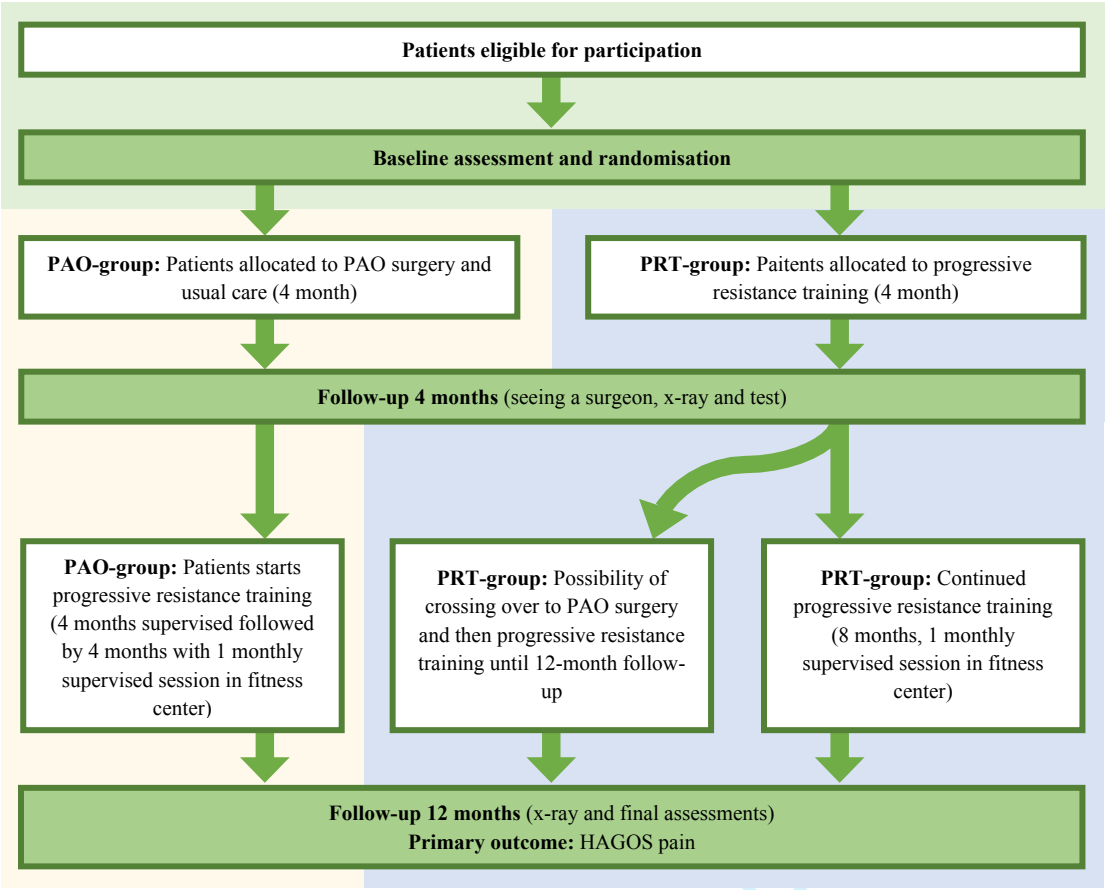
The PRT group receives 4 months of supervised PRT 2 times per week. A physiotherapist or physiotherapist student will supervise all training sessions the first 4 weeks. The following 4 weeks, 6 out of 8 training sessions are supervised and from week 9-16, half of the training sessions (8 out of 16) are supervised. After these 4 months (16 weeks), patients receive a free membership to a fitness center near their home address and are encouraged to train on their own twice per week until 12 months follow-up with one supervised session per month. Supervised training sessions will be conducted at VIA

University College (in Denmark) or at a physiotherapy practice (in Norway). If the included patients randomised to the PRT group do not find they benefit from the PRT they can crossover from 4 months (see Figure 1 and the section "Anchor question"), or at any time later throughout the intervention. Four months is the normal time to wait when being on the waiting list for a PAO surgery, but if patients wish to crossover after 4 months of PRT, they will not be put on a new waiting list but directly scheduled for PAO.

PAO-group:

PAO will be performed with the trans-sartorial approach (5) or the anterior pelvic approach (4). X-rays (AP pelvic and AP hip) will be performed at 6 weeks, 4 months and 12 months. Patients commence post-operative rehabilitation as usual and follow the rehabilitation program guided by a physiotherapist specialized in hip problems until 4 months after the operation. Four months postoperative the patients complete usual care and commence with the same PRT intervention program as the PRT group, until 12 months follow-up (see description above).

Figure 1.
Patient flow through the trial



METHOD

Training program

The PRT program involves 10-min of warm up followed by 4 exercises including sets of loaded squats, hip extension, hip flexion, and hip abduction. Loaded squat is performed standing with a barbell or dumbbells and target hip- and knee- extensors and flexors. Hip extension is performed standing in a cable-tower with a cable fixed around the ankle and the leg is moved backward and upward in a stretched position to perform hip-extension against resistance. Hip flexion is performed standing in a cable-tower with the cable fixed around the ankle and the knee is moved forward and upward to perform hip-flexion against resistance. Hip abduction is performed standing in a cable-tower with a cable fixed around the leg and leg is moved out to the side and up while kept stretched, to perform hip-abduction against resistance. To avoid muscle soreness of the affected leg (defined as index leg), squat is performed before the unilateral exercises. After week 16, all exercises are performed by both legs to train stability for the index leg and because the majority of the patients have bilateral hip dysplasia and hence probably profit

from bilateral resistance training. The exercises are focused on strengthening all the muscles around the hip. Since patients with hip dysplasia primarily experience decreased strength in hip flexors and hip abductors (26) these muscles are incorporated in the training program, but to assure a symmetrical strengthening of the hip muscles, hip extensors are also included in the training program. Only 4 exercises have been included in the training program to ensure that the training sessions do not exceed 60 minutes, and consequently patients are more likely to adhere to the training program. The exercises are simple to perform, and all equipment used are standard equipment in essentially all fitness centres. The absolute training load will be individually adjusted on a set-by-set basis, using the plus two principle (if the patient is able to perform two or more repetitions than required, the load is increased). Hip related pain levels up to 5 on the VAS is considered acceptable during exercise (11). Progression of relative load will be performed as described in table 1.

Table 1.
Progressive resistance training descriptions over the 12 months intervention period

Exercise variable	Week 1-2	Week 3-4	Week 5-52	Week 7-52
Load	15 RM[b]	12 RM	10 RM	8 RM
Repetitions	10	12	10	8
Set per session	3	3	4	4
Rest between sets	90 sec.	90 sec.	120 sec.	120 sec.
Sessions per week	2	2	2	2
Duration of training period	52 weeks	52 weeks	52 weeks	52 weeks
Exercises	Loaded squat	Loaded squat	Loaded squat	Loaded squat
	Hip extension	Hip extension	Hip extension	Hip extension
	Hip flexion	Hip flexion	Hip flexion	Hip flexion
	Hip abduction	Hip abduction	Hip abduction	Hip abduction
Contraction failure in each set	Yes	Yes	Yes	Yes
Range of motion	Maximal possible	Maximal possible	Maximal possible	Maximal possible
Rest between training sessions	>36 h	>36 h	>36 h	>36 h

After week 16, all exercises are performed by both legs. [b]Repetition Maximum (RM).

Outcomes

Outcome assessments will be performed at baseline, and at 4-months and 12-months follow-up (after initiation of surgical/non-surgical treatment). An assessor blinded to group allocation will conduct baseline and follow-up measurements. Five and 10 years after inclusion into the trial, the patients will be contacted and asked to complete hip-related questionnaires. An overview of the different outcomes is presented in Table 3.

Primary outcome:

The pain subscale of the patient-reported questionnaire HAGOS, were the total score ranges from 0 (worst) to 100 (best) (26). HAGOS is a valid, reliable, and responsive patient-reported outcome in young patients with hip and groin related pain (26). A minimal clinically relevant difference of the HAGOS pain subscale is considered to be 9.7 (27).

Secondary outcome:

The most important secondary outcomes are presented as key secondary outcomes. The key secondary outcomes are the other subscales of the HAGOS covering Symptoms, Physical function in daily living, Physical function in Sport and Recreation and Quality of Life; Single leg hop for distance (SLH) (28,29); adverse and serious adverse events (Table 2). Usage of painkillers (yes/no) and type of analgesics is also part of the key secondary outcomes. The other secondary outcomes are; HAGOS subscale Participation in Physical Activities; pain reported by the Visual Analogue Scale (VAS) (30); Forgotten joint score-12 (FJS-12) (31); Y-balance test (YBT) (32); and isometric measured hip muscle strength (flexion, extension and abduction).

Exploratory outcomes: Tri-axial accelerometer (only at baseline and 12-months follow-up); EuroQol Group 5-dimension self-report questionnaire with 5 levels (EQ-5D-5L) (33); delay to surgery and demographic differences between crossover patients compared to patients as treated in the PRT group.

Demographic data: Gender, age, height, weight, duration of hip symptoms, civil status, educational level, employment status, physical activity and exercise, alcohol intake, smoking behaviours and co-morbidities.

Assessment of compliance: Compliance to training will be registered from the patients' training protocols, described as number of sessions attended vs. number of planned sessions according to the protocol in per cent. Compliance to training will be calculated both for those who complete the intervention and for all patients, including drop-outs. High compliance is defined as ≥70% attendance to the supervised sessions the first 4 months. Number of self-training sessions will be recorded in a training diary and high compliance to self-training (from 4 to 12 months follow-up) is defined as attendance to the PRT of ≥50%.

X-rays: X-rays will be performed with the patient in standing position (AP pelvic) and in supine position (AP hip), at baseline and 4-months and 12-months follow-up for both groups. X-rays will also be repeated at 6 weeks for the PAO-group as part of the standard postoperative care.

Data entry: In Denmark the software REDCap will be used for data entering, while EpiData will be used in Norway.

Table 2.
Adverse and serious adverse events (34).

Adverse events
Haematoma
Delayed wound closure
Dysaethesia of lateral femoral cutaneous nerve
Malpositioning; retroversion or insufficient reorientation. Insufficient reorientation (coverage) – optimally is the CE angle 30-40 degrees and the AI angle 0-10 degrees.
Heterotopic ossifications (Brooker I and II)
Urinary tract infections
Infection not requiring surgical revision
Serious adverse events
Avascular necrosis of the femoral head or acetabulum
Nerve palsy
Major bleeding (administration of more than 5 blood units intra- and postoperatively)
Peroneal and femoral neurapraxia
Deep vein thrombosis
Pulmonary embolism
Stress fracture of ischial bone and posterior column
Intraarticular osteotomy
Heterotopic ossifications (Brooker III and IV)
Infection requiring surgical revision
Loss of fixation/loss of reorientation
Delayed or non-union of pubic, ischial or iliac bone

Protocol article version 4. 12.07.19

Table 3.
Assessments and procedures

	Baseline	Surgery	4 months	12 months	5 years	10 years
Baseline characteristics						
Gender	X					
Age	X					
Height	X					
Weight	X		X	X		
Duration of hip symptoms	X					
Marital status	X					
Educational level	X					
Employment status	X					
Physical activity and exercise	X		X	X		
Alcohol intake	X					
Smoking behaviors	X					
Co-morbidities	X					
Patient-reported outcomes						
HAGOS[a]	X		X	X	X	X
EQ-5D-5L[b]	X		X	X	X	X
FJS-12[c]	X		X	X	X	X
Anchor questions			X	X		
Physical performance tests						
Single leg hop for distance	X		X	X		
Y-balance test	X		X	X		
Isometric hip muscle strength[d]	X		X	X		
Physical activity						
Tri-axial accelerometry	X			X		
Treatment related variables						
X-ray	X		X	X		
Adverse events[e]			X	X		
Serious adverse events[e]			X	X		
Training-compliance			X	X		
Visual Analog scale[f]	X		X	X		
Other treatments			X	X		
Usage of analgesics	X		X	X		
Delay to surgery (only PRT-group)					X	X
Surgery (only PRT-group)			X	X	X	X

[a]The Copenhagen Hip and Groin Outcome Score (HAGOS). [b]European Quality of life 5 Dimensions with 5 Levels (EQ-5D-5L). [c]Forgotten Joint Score (FJS-12). [d]Isometric hip muscle strength: hip flexion, extension and abduction. [e]See Table 2. [f]VAS scores will be obtained before and after training.

Anchor question

After 4 months, the patients will have an appointment with the surgeon. Before this meeting the patients will fill out the anchor question (described below) and the HAGOS questionnaire. These two questionnaires will form the basis of the talk with the surgeon. For patients allocated to the PRT group, the surgeon will ask the patient to evaluate to which extent the a priori hip problems have been addressed, and the patient and surgeon decide whether the patient continues in the PRT group they have been randomised to or is crossing-over to PAO. The decision of crossing-over is thus a decision made between the surgeon and the patient, based on the anchor question and the HAGOS questionnaire. After talking to the surgeon, function and muscle strength will be tested.

Anchor question

PAO-group: How is your operated hip now compared to before surgery? Much better, slightly better, the same, slightly worse or much worse?

PRT-group: How is your hip now compared to before you started this training program? Much better, slightly better, the same, slightly worse or much worse?

Sample size

A minimal clinically relevant difference of the HAGOS pain subscale is considered to be 9.7 (27). Based on a previous pilot trial the standard deviation of HAGOS pain in PAO patients is 16.2 (14). Given a power of 0.80 and two-sided significance level α=0.05, the estimated sample size of each intervention group is 44 patients. Allowing for possible crossovers and loss to follow-up, the number of included patients in each intervention group will be 48 patients.

Data availability statement

Aarhus University Hospital is responsible for handling all personal data provided by both sites in accordance to the Clinical Trial Agreement and the EU General Data Protection Regulation (GDPR). Oslo University Hospital agree that information directly related to the protocol and trial, including data, material, Intellectual Property and results generated from the trial shall be the property of Aarhus University Hospital, and shall be treated in strict confidence, and shall not be disclosed to any third party, or use for its benefit or the benefit of any third party, without the prior written consent of Aarhus University Hospital, except for data that is (i) publicly known or available from other sources who are not under a confidentially obligation to the other party; (li) has been made available by the other party without confidentiality obligation; or (iii) is independently developed or otherwise already known by or available to the other party without a confidentiality obligation; or (iv) is already required disclosed by law.

Statistical considerations

The primary efficacy analysis will be assessment of the between-group difference in change in the HAGOS pain subscale from baseline to 6 months after initiating the treatment (primary end-point). All descriptive statistics and tests will be reported in accordance with the recommendations of the *"Enhancing the QUAlity and Transparency Of health Research"* (EQUATOR) (35) network and the CONSORT statement (25). The primary analysis will follow the intention-to-treat principle. Sensitivity and exploratory analysis will be performed with the purposes to test the robustness of the results per-protocol with good compliance (defined as participation in ≥70% of the training sessions) and as-treated analysis, in which patients will be analysed based on their adherence to the randomised treatment expecting three groups: (1) patients randomised to PAO, (2) patients randomised to PRT without undergoing PAO in the follow-up period, (3) patients randomised to PRT undergoing PAO in the follow-up period.

Ethics and dissemination

The trial is approved by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-234-18) and by the Danish Data Protection Agency (Journal No 1-16-02-120-19). The trial is also approved by The Regional Committee for Medical and Health Research Ethics, Region South-East Norway (Ref. 2018/1603). The trial is registered at Clinical Trial (NCT03941171). Before inclusion, all patients will have to give their written, informed consent in accordance with the Declaration of Helsinki II. All data and information collected in regard to this trial will be treated confidentially by the researchers and staff connected to the trial.

Patient and public involvement

During the development of the trial design, we have interviewed a group of patients with hip dysplasia with the purpose of gaining knowledge on the patients' thoughts on participating in a clinical trial that investigates the efficacy of joint preserving surgery compared to a PRT program. The patients were asked to consider how often they would be able to train, how far they would be willing to commute to the training facility and what their primary reason for seeking treatment had been. Likewise, they were asked about what was most important for them to achieve with an operation or a training intervention. This was performed in order to use the obtained knowledge to improve our patient information, the method of patient recruitment and the PRT program.

DISCUSSION

This is the first head-to-head comparison to evaluate the additive effect of PAO in addition to non-surgical treatment in patients with hip dysplasia scheduled for PAO. The trial will provide valuable evidence to surgeons, physiotherapists, and decision makers by highlighting the efficacy, benefits and harms of the surgical and non-surgical treatment approach, respectively. The results are expected to have an immediate substantial impact on clinical practise.

Since the trial is designed to be an assessor blinded randomised controlled trial, it reaches the highest evidence level. For obviously reasons it is not possible to blind the patients towards the intervention, which is a limitation of the trial. The trial is conducted at two University Hospitals and the patients are regular patients, thus the infrastructure used is of high standard. Both hospitals have specific hip units and have all necessary hospital equipment available including operational environment and post-operative hospitalization. All outcomes are valid and reliable outcome measures and consist of both multiple patient-reported outcomes and objective outcome measures.

There can be unforeseen risks in connection with all trials, but these are considered minimal in this trail. When performing PRT, it is normal to experience muscle soreness, and based on the experience from our earlier feasibility trial (14) testing PRT in patients with hip dysplasia, we know that there are times where the patients can experience muscle-related pain. The patients are thus asked to score their pain before and after each training session, to ensure that the training does not aggravate the hip pain. All methods included in this trial have been used in previous approved trials.

All results from the trial will be published in international peer-reviewed scientific journals regardless of whether the results are positive, negative or inconclusive.

Author contributions

Lisa Reimer, Stig Jakobsen, Louise Mortensen, Ulrik Dalgas, Julie Jacobsen, Kjeld Søballe, Tone Bere, Jan Madsen, Lars Nordsletten, May Risberg and Inger Mechlenburg were a part of designing the trial and approved the final version of the protocol. Lisa Reimer and Inger Mechlenburg wrote the protocol and Stig Jakobsen, Louise Mortensen, Ulrik Dalgas, Julie Jacobsen, Kjeld Søballe, Tone Bere, Jan Madsen, Lars Nordsletten and May Risberg revised the protocol.

Data statement

After publishing, data regarding Danish patients will be stored at The Danish National Archives, while the data regarding Norwegian patients will be stored at The Norwegian National Archives. With the right approvals data can be accessed there.

Funding

This trial is supported by Aase and Ejnar Danielsens Foundation (84,000 dkk), Alfred Benzons Foundation (1,164,000 dkk), Andelsforeningernes Humanitære og Kulturelle Fond (20,000 dkk), Fondsstiftelsen ved Oslo Universitetssykehus (148.000 nok), The Danish Rheumatism Association (265,000 dkk), The Family Hede Nielsens Foundation (10,000 dkk), The Norwegian Fund for Post-

Graduate Training in Physiotherapy (252.000 nok) and Vanførefonden (100,000 dkk). The foundations had no role in planning the trial and did only deliver financial support.

Conflict of interest

None declared.

Ethics approval

The Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-234-18), the Danish Data Protection Agency (Journal No 1-16-02-120-19) and The Regional Committee for Medical and Health Research Ethics, Region South-East Norway (Ref. 2018/1603) approved the trial.

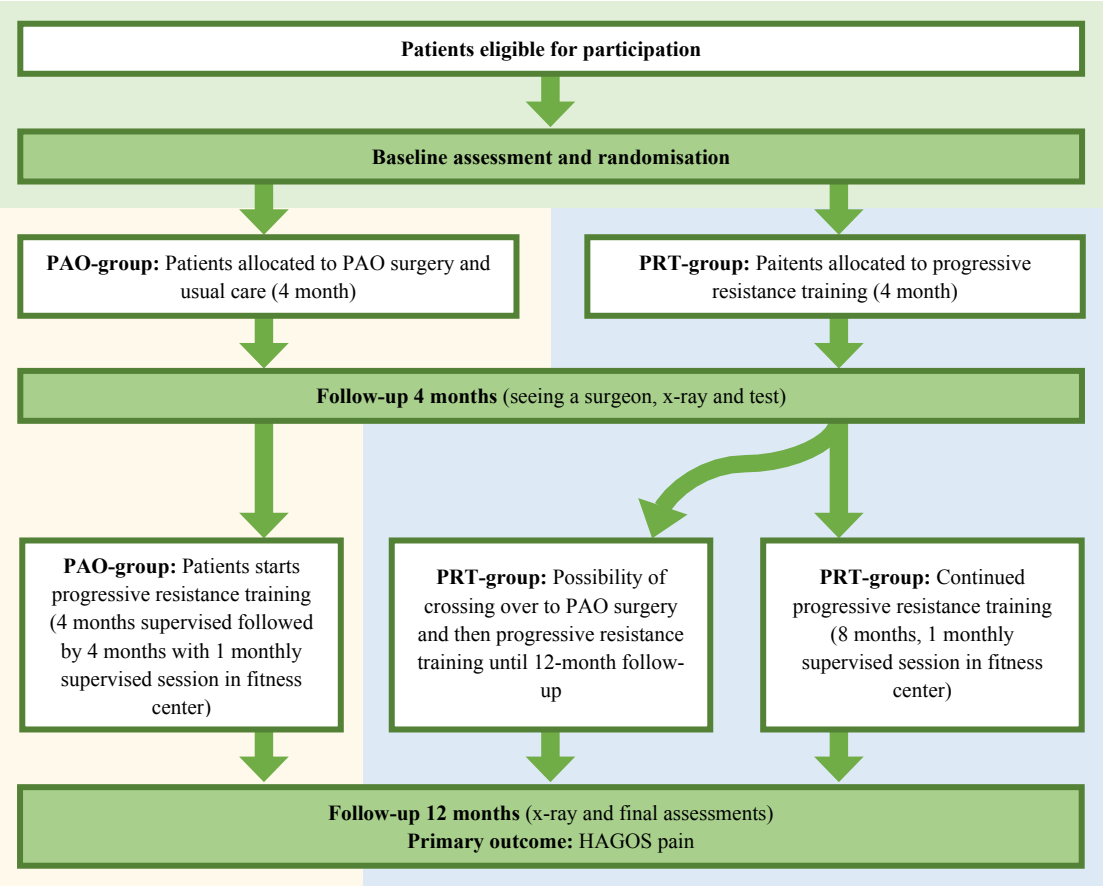
REFERENCES

1. Murphy SB, Ganz R, Muller ME. The prognosis in untreated dysplasia of the hip. A study of radiographic factors that predict the outcome. J Bone Jt Surgery Am Vol. 1995;77(7):985–9.
2. Jacobsen S, Sonne-Holm S. Hip dysplasia: a significant risk factor for the development of hip osteoarthritis. A cross-sectional survey. Rheumatology. 2005;44(2):211–8.
3. Wyles CC, Heidenreich MJ, Jeng J, Larson DR, Trousdale RT, Sierra RJ. The John Charnley Award: Redefining the Natural History of Osteoarthritis in Patients With Hip Dysplasia and Impingement. Clin Orthop Relat Res. 2017;475:336–50.
4. Ganz R, Klaue K, Vinh TS, Mast JW. A new periacetabular osteotomy for the treatment of hip dysplasias. Technique and preliminary results. Clin Prthop Relat Res. 1988;232:26–36.
5. Troelsen A, Elmengaard B, Soballe K. A new minimally invasive transsartorial approach for periacetabilar osteotomy. J Bone Jt Surgery Am Vol. 2008;90(3):493–8.
6. Steppacher SD, Tannast M, Ganz R, Siebenrock KA. Mean 20-year Followup of Bernese Periacetabular Osteotomy. Clin Orthop Relat Res. 2008;466(7):1633–44.
7. Lerch TD, Steppacher SD, Liechti EF, Tannast M, Siebenrock KA. One-third of Hips After Periacetabular Osteotomy Survive 30 Years With Good Clinical Results, No Progression of Arthritis, or Conversion to THA. Clin. 2017;475(4):1154–68.
8. Hartig-Andreasen C, Troelsen A, Thillemann TM, Søballe K, Hartvig-Andreasen C, Troelsen A, et al. What Factors Predict Failure 4 to 12 Years After Periacetabular Osteotomy? Clin Orthop Relat Res. 2012;470(11):2978–87.
9. Mechlenburg I, Nyengaard JR, Gelineck J, Soballe K. Cartilage Thickness and Cyst Volume Are Unchanged 10 Years After Periacetabular Osteotomy in Patients Without Hip Symptoms. Clin Orthop Relat Res. 2015;473(8):2644–9.
10. Mechlenburg I, Nyengaard JR, Rømer L, Søballe K. Changes in load-bearing area after Ganz periacetabular osteotomy evaluated by multislice CT scanning and stereology. Acta Orthop Scand. 2004;75(2):147–53.
11. Jacobsen S, Sonne-Holm S, Soballe K, Gebuhr P, Lund B. Joint space width in dysplasia of the hip: a case-control study of 81 adults followed for ten years. J Bone Jt Surg. 2005;87(4):471–7.
12. Troelsen A, Romer L, Soballe K. [Hip dysplasia: clinical assessment, radiologic evaluation and reference]. Ugeskr Laeger. 2007;169(5):394–6.
13. Sørensen H, Nielsen DB, Jacobsen JS, Søballe K, Mechlenburg I. Isokinetic dynamometry and gait analysis reveal different hip joint status in patients with hip dysplasia. HIP Int. 2019;29(2):215–21.
14. Mortensen L, Schultz J, Elsner A, Jakobsen SS, Søballe K, Jacobsen JS, et al. Progressive resistance training in patients with hip dysplasia: A feasibility study. J Rehabil Med. 2018;50(8):751–8.
15. Clohisy JC, Nepple JJ, Ross JR, Pashos G, Schoenecker PL. Does Surgical Hip Dislocation and Periacetabular Osteotomy Improve Pain in Datients with Perthes-like deformities and Acetabular Dysplasia? Clin Orthop Relat Res. 2015;473(4):1370–7.
16. Kanai A, Kiyama T, Genda E, Suzuki Y. Biomechanical investigation of ambulatory training in patients with acetabular dysplasia. Gait Posture. 2008;28(1):52–7.
17. Kuroda D, Maeyama A, Naito M, Moriyama S, Yoshimura I, Nakamura Y, et al. Dynamic hip stability, strength and pain before and after hip abductor strengthening exercises for patients with dysplastic hips. Isokinet Exerc Sci. 2013;21(2):95–100.

18. Harris-Hayes M, Czuppon S, Van Dillen LR, Steger-May K, Sahrmann S, Schootman M, et al. Movement Pattern Training To Improve Function in People with Chronic Hip Joint Pain: A Feasibility Randomized Clinic Trial. J Orthop Sport Phys Ther. 2016;46(6):452–61.
19. Bieler T, Siersma V, Magnusson SP, Kjaer M, Christensen HE, Beyer N. In hip osteoarthritis, Nordic Walking is superior to strength training and home-based exercise for improving function. Scand J Med Sci Sport. 2017;27(8):873–86.
20. Hermann A, Holsgaard-Larsen A, Zerahn B, Mejdahl S, Overgaard S. Preoperative progressive explosive-type resistance training is feasible and effective in patients with hip osteoarthritis scheduled for total hip arthroplasty - a randomized controlled trial. Osteoarthr Cartil. 2016;24(1):91–8.
21. Wartolowska K, Judge A, Hopewell S, Collins GS, Dean BJF, Rombach I, et al. Use of placebo controls in the evaluation of surgery: systematic review. BMJ [Internet]. 2014;348:g3253. Available from: http://dx.doi.org/doi:10.1136/bmj.g3253
22. Wartolowska K, Beard DJ, Carr AJ. Attitudes and Beliefs about Placebo Surgery among Orthopedic Shoulder Surgeons in the United Kingdom. PLoS One. 2014;9(3):e91699.
23. Zurmuhle CA, Anwander H, Albers CE, Hanke MS, Steppacher SD, Siebenrock KA, et al. Periacetabular Osteotomy Provides Higher Survivorship Than Rim Trimming for Acetabular Retroversion. Clin Orthop Relat Res. 2017;475(4):1138–50.
24. Belzile EL, Beaule PE, Ryu J-J, Clohisy JC. Outcomes of joint preservation surgery: comparison of patients with developmental dysplasia of the hip and femoroacetabular impingement. J Hip Preserv Surg. 2016;3(4):270–7.
25. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010;63(8):e1–37.
26. Thorborg K, Holmich P, Christensen R, Petersen J, Roos EM, Hölmich P, et al. The Copenhagen Hip and Groin Outcome Score (HAGOS): development and validation according to the COSMIN checklist. Br J Sport Med. 2011;45(6):478–91.
27. Thomeé R, Jónasson P, Thorborg K, Sansone M, Ahldén M, Thomeé C, et al. Cross-cultural adaptation to Swedish and validation of the Copenhagen Hip and Groin Outcome Score (HAGOS) for pain, symptoms and physical function in patients with hip and groin disability due to femoro-acetabular impingement. Knee Surg Sport Traumatol Arthrosc. 2014;22(4):835–42.
28. Ageberg E, Cronström A. Agreement between test procedures for the single-leg hop for distance and the single-leg mini squat as measures of lower extremity function. BMC Sports Sci Med Rehabil. 2018;10:15:1–7.
29. Kemp JL, Risberg MA, Schache AG, Makdissi M, Pritchard MG, Crossley KM. Patients With Chondrolabral Pathology Have Bilateral Functional Impairments 12 to 24 Months After Unilateral Hip Arthroscopy: A Cross-sectional Study. J Orthop Sport Phys Ther. 2016;46(11):947–56.
30. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. Arthritis Care Res. 2011;63(SUPPL. 11):S240–52.
31. Behrend H, Giesinger K, Giesinger JM, Kuster MS. The “Forgotten Joint” as the Ultimate Goal in Joint Arthroplasty. Validation of a New Patient-Reported Outcome Measure. J Arthroplasty. 2012;27(3):430-436.e1.

32. Plisky PJ, Gorman PP, Butler RJ, Kiesel KB, Underwood FB, Elkins B. The reliability of an instrumented device for measuring components of the star excursion balance test. North Am J Sport Phys Ther. 2009;4(2):92–9.
33. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36.
34. Biedermann R, Donnan L, Gabriel A, Wachter R, Krismer M, Behensky H. Complications and patient satisfaction after periacetabular pelvic osteotomy. Int Orthop. 2008;32(5):611–7.
35. Christensen R, Bliddal H, Henriksen M. Enhancing the reporting and transparency of rheumatology research: A guide to reporting guidelines. Arthritis Res Ther. 2013;15(1):1–4.

Figure 1.
Patient flow through the study



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	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
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 + 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	14
Roles and responsibilities: committees	#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)	4
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	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	4
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	4

		collected. Reference to where list of study sites can be obtained	
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)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#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)	5 + 12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	8-11
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)	7
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	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4

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	5
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	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#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 plan	#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	7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for	n/a

		participants who discontinue or deviate from intervention protocols	
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	9
Statistics: outcomes	#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	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
Statistics: analysis population and missing data	#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)	12
Methods: Monitoring			
Data monitoring: formal committee	#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. No monitoring in this study
Data monitoring: interim analysis	#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. No monitoring in this study
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	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a. No auditing in this study
Ethics and dissemination			

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#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	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
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	n/a
Dissemination policy: trial results	#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	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a

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

Notes:

- 21a: n/a. No monitoring in this study
- 21b: n/a. No monitoring in this study
- 23: n/a. No auditing in this study This checklist was completed on 05. July 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

The efficacy of Periacetabular osteotomy followed by progressive resistance training compared to progressive resistance training as non-surgical treatment in patients with Hip dysplasia (PreserveHip). A protocol for a randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032782.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Nov-2019
Complete List of Authors:	Reimer, Lisa; Aarhus University Hospital, Orthopedic Surgery Jakobsen, Stig; Aarhus University Hospital, Orthopedic Surgery Mortensen, Louise; Aarhus University Hospital, Orthopedic Surgery Dalgas, Ulrik; Aarhus University, Public Health - Sport Jacobsen, Julie; VIA University College, Physiotherapy & Research Centre for Health and Welfare Technology, Programme for Rehabilitation Soballe, Kjeld; Aarhus University Hospital, Orthopedic Surgery Bere, Tone; Oslo University Hospital, Orthopedic Surgery Madsen, Jan; Oslo University Hospital, Orthopedic Surgery Nordsletten, Lars; Oslo University Hospital, Orthopedic Surgery; University of Oslo, Faculty of Medicine Risberg, May Arna; Oslo University Hospital, Orthopedic Surgery Mechlenburg, Inger; Aarhus University Hospital, Orthopedic Surgery; Aarhus University, Clinical Medicine
Primary Subject Heading:	Public health
Secondary Subject Heading:	Sports and exercise medicine
Keywords:	Hip dysplasia, Periacetabular Osteotomy, PAO, Progressive Resistance Training, Osteoarthritis, Hip < ORTHOPAEDIC & TRAUMA SURGERY

Protocol article version 8.11.19

The efficacy of Periacetabular osteotomy followed by progressive resistance training compared to progressive resistance training as non-surgical treatment in patients with Hip dysplasia (PreserveHip). A protocol for a randomised controlled trial.

Researchers and institutions
Lisa Cecilie Urup Reimer[a], MSc, lisareimer@clin.au.dk
Stig Storgaard Jakobsen[a], PhD, stig.jakobsen@clin.au.dk
Louise Mortensen[a], MSc, lpmortensen@hotmail.com
Ulrik Dalgas[b], PhD, dalgas@ph.au.dk
Julie Sandell Jacobsen[c], MSc, jsaj@via.dk
Kjeld Søballe[a], DMSc, kjeld@soballe.com
Tone Bere[d], PhD, bereto@ous-hf.no
Jan Erik Madsen[d], PhD, j.e.madsen@medisin.uio.no
Lars Nordsletten[de], PhD, lars.nordsletten@medisin.uio.no
May Arna Risberg[d], PhD, m.a.risberg@nih.no
Inger Mechlenburg[af], PhD, DMSc, inger.mechlenburg@clin.au.dk

[a]Department of Orthopedic Surgery, Aarhus University Hospital, Denmark.
[b]Department of Public Health – Sport, Aarhus University, Denmark
[c]Department of Physiotherapy & Research Centre for Health and Welfare Technology, Programme for Rehabilitation, VIA University College, Denmark
[d]Department of Orthopedic Surgery, Oslo University Hospital, Norway
[e]Faculty of Medicine, University of Oslo, Norway
[f]Department of Clinical Medicine, Aarhus University, Denmark

Corresponding author
Name: Lisa Cecilie Urup Reimer
Adress: Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark
E-mail: lisareimer@clin.au.dk
Phone: +45 26 47 40 80

Word count
3.473 words

Protocol article version 8.11.19

ABSTRACT

Introduction

Periacetabular osteotomy (PAO) is an established treatment for adolescent and adult patients with hip dysplasia. However, the efficacy of PAO has not been tested against another surgical intervention or conservative treatment in a randomised controlled trial before. We suggest that progressive resistance training (PRT) could be an alternative to PAO. The primary aim of this trial is therefore to examine the efficacy of PAO followed by 4 months of usual care followed by 8 months of PRT compared to 12 months of solely PRT in patients with hip dysplasia eligible for PAO in terms of patient-reported pain measured by The Copenhagen Hip and Groin Outcome Score (HAGOS).

Methods and analysis

This trial is a single blinded multicentre randomised controlled clinical trial, where patients with hip dysplasia, who are eligible for PAO, will be randomised to either PAO followed by usual care and PRT or PRT only. Primary outcome is patient-reported pain, measured on the subscale pain on the Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire 12 months after initiation of PAO or PRT. The key secondary outcomes are the other subscales of the HAGOS, adverse and serious adverse events, usage of painkillers (yes/no) and type of analgesics. Based on the sample size calculation, the trial needs to include 96 patients.

Ethics and dissemination

The trial is approved by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-234-18) and by the Danish Data Protection Agency (Journal No 1-16-02-120-19). The trial is also approved by The Regional Committee for Medical and Health Research Ethics, Region South-East Norway (Ref. 2018/1603). All results from this trial will be published in international peer-reviewed scientific journals regardless of whether the results are positive, negative or inconclusive.

Trial registration

The trial is registered at Clinical Trial (NCT03941171).

Keywords

Hip dysplasia, Periacetabular Osteotomy, PAO, Progressive Resistance Training, Osteoarthritis

Protocol article version 8.11.19

ARTICLE SUMMARY

Strengths and limitations of this trial

- This is the first head-to-head comparison to evaluate the additive effect of PAO in addition to non-surgical treatment in patients with hip dysplasia scheduled for PAO.
- The trial will provide valuable evidence to surgeons, physiotherapists, and decision makers by highlighting the efficacy, benefits and harms of the surgical and non-surgical treatment approach, respectively.
- The results are expected to have an immediate substantial impact on clinical practise by providing new evidence to achieve optimal allocation of health care resources as well as markedly improved knowledge when informing patients with hip dysplasia about their options.
- The trial is a multicentre randomised controlled and assessor blinded trial, conducted at two sites in two countries.
- A limitation is that the patients cannot be blinded towards the intervention.

INTRODUCTION

Hip dysplasia is associated with development of early osteoarthritis (OA) (1–3). However, not everyone with radiologically verified hip dysplasia develops OA. Periacetabular osteotomy (PAO) (4,5) is an established treatment for hip dysplasia in adolescents and adults (6–9). The aim of PAO is to improve pain and prevent secondary OA by improvement the hip biomechanics (10). However, studies describing the natural history of hip dysplasia are lacking. The lack of knowledge is problematic since patients are offered a surgery with potential complications mainly based on pain indication without knowing if OA would progress. In a longitudinal trial, 136 controls were compared with 81 persons with mild or moderate radiological verified hip dysplasia (11). The participants were followed for a decade, but the results of the study did not document a tendency for radiological hip degeneration. In contrast, Morita et al. (12) found that the probability of OA progression was 13% in a cohort of 88 patients with hip dysplasia who had received a rotational acetabular osteotomy in the contralateral hip 20 years earlier.

Patients with hip dysplasia typically experience hip pain and reduced walking distance. The pain is localised to the groin area and can be sharp, sudden and sometimes radiate towards the knee (13). This results in reduced patient-reported and performance-based physical function (7,8,14–16). In addition, Sørensen et al. (14) showed that patients with hip dysplasia had weaker hip flexor and abductor muscles than age and gender matched controls. Only few trials have investigated physical training for this patient group (17–19). Importantly, trials in hip OA (20,21) have shown, that progressive resistance training (PRT) seems to be a promising exercise modality that may relieve pain and improve function. To our knowledge, no trials have applied PRT in hip dysplasia. We therefore performed a pilot PRT trial (15) on 17 patients with hip dysplasia scheduled for PAO and found that PRT is feasible with few and minor adverse events and that the patients were motivated for the training (high training compliance). The pilot trial further indicated decreased patient-reported pain, symptoms and better patient-reported scores for

sport and recreation measured by The Copenhagen Hip and Groin Outcome Score (HAGOS). Moreover, we found increased performance-based function and increased hip flexion muscle strength on the affected side. As such, a well-powered RCT comparing PRT to PAO in hip dysplasia seems justified.

In further support of the afore mentioned RCT, patients, their relatives, health care providers and decision makers have a common interest in investigating the efficacy of PAO. As described by Wartolowska et al. (22), it is reasonable to assume that surgery is associated with a placebo effect. Firstly, because invasive procedures have a stronger placebo effect than non-surgical ones and, secondly, because a confident diagnosis and a decisive approach to treatment, typical for surgery, usually results in a strong placebo effect (22). A recent survey (23) among British shoulder surgeons showed that surgeons generally agreed that a placebo component to surgical intervention might exist. With the increased use of PAO worldwide and expanded indications for PAO, such as acetabular retroversion and femoroacetabular impingement syndrome (16,24,25), it is problematic that the efficacy of PAO has not been investigated in a randomised controlled trial.

Aim and hypothesis of the trial

The primary aim of this trial is to examine the efficacy of PAO followed by 4 months of usual care followed by 8 months of PRT compared to 12 months of a PRT only, in patients with hip dysplasia eligible for PAO, in terms of patient-reported pain measured by HAGOS. Secondary aims are to investigate changes in patient-reported symptoms, physical function in daily living, physical function in sport and recreation, hip and/or groin-related quality of life, generic health status, performance-based function, hip muscle strength, physical activity and adverse events between PAO followed by usual care and PRT compared to PRT only. We hypothesise that PAO followed by usual care and PRT results in significantly less pain at 12 months follow-up compared to PRT only.

MATERIAL

Design

This trial is a multicentre randomised controlled and assessor blinded trial, following the CONSORT guidelines (26). Change in primary outcome will be measured from baseline to 12-months follow-up, while change in secondary outcomes will be measured from baseline to 4 and 12-months follow-up. In addition, 5-year and 10-year follow-up with questionnaires is planned.

Patients

Setting and location: Patients will be recruited from the Departments of Orthopaedic Surgery at Aarhus University Hospital, Denmark and at Division of Orthopaedic Surgery at Oslo University Hospital, Norway. Approximately 130 PAOs are performed yearly in Aarhus, and 40 PAO are performed in Oslo yearly. We expect to recruit 96 patients. Both centers will be including patients, but the analysis will be performed at Aarhus University Hospital.

Eligibility criteria:

1. Patients aged 18-40 years and diagnosed with hip dysplasia referred from primary care to the Department of Orthopaedic Surgery at one of the two participating hospitals.
2. Considered eligible for PAO by a surgeon.
3. Radiographically verified hip dysplasia (CE-angle <25 degrees and AI-angle >10 degrees) and clinical symptoms.
4. Range of motion: internal rotation >15 degrees, external rotation >15 degrees, hip flexion >110 degrees.
5. Able to drive or commute to training sessions.

Exclusion criteria:

1. OA degree >1 on classification of Tönnis.
2. CE-angle <10 degrees.
3. Retroverted acetabulum (cross over sign and posterior wall sign).
4. Previous pelvic surgery for hip dysplasia (affected side).
5. Calvé Legg Perthes or epifysiolysis.
6. Simultaneous bilateral PAO.
7. Previous surgery for herniated disc, spondylodesis, arthroplasty of hip, knee or ankle.
8. Previous surgery of the hip (tenotomy of iliopsoas tendon, z-plastic of the iliotibial tract or hip arthroscopy) in index leg.
9. Neurological or rheumatoid diseases that affect the hip function.
10. Inadequacy in written and spoken Danish or Norwegian.
11. Body Mass Index (BMI) >25.

Randomisation

After baseline assessment, the patients will be randomised in a 1:1 ratio to either PAO followed by usual care and PRT (PAO-group) or PRT only (PRT-group). A computer-generated list of random numbers will be set up in the Research Electronic Data Capture (REDCap) randomise tool. Administrators of the randomisation procedure will be blinded to block sizes and randomisation sequence at all times during the trial period. Allocation concealment will be ensured, as the randomisation will not be performed and revealed before the patient has been irreversibly included in the trial. After randomisation a secretary or project coordinator, who is otherwise not affiliated with the trial, will refer patients to surgery or to the treating physiotherapist/physiotherapy student who contacts the patient for an appointment of the first exercise session.

PRT-group:

The PRT group receives 4 months of supervised PRT 2 times per week. A physiotherapist or physiotherapist student will supervise all training sessions the first 4 weeks. The following 4 weeks, 6

out of 8 training sessions are supervised and from week 9-16, half of the training sessions (8 out of 16) are supervised. After these 4 months (16 weeks), patients receive a free membership to a fitness center near their home address and are encouraged to train on their own twice per week until 12 months follow-up with one supervised session per month. Supervised training sessions will be conducted at VIA University College (in Denmark) or at a physiotherapy practice (in Norway). If the included patients randomised to the PRT group do not find they benefit from the PRT they can crossover from 4 months (see Figure 1 and the section "Anchor question"), or at any time later throughout the intervention. Four months is the normal time to wait when being on the waiting list for a PAO surgery, but if patients wish to crossover after 4 months of PRT, they will not be put on a new waiting list but directly scheduled for PAO.

PAO-group:

PAO will be performed with the trans-sartorial approach (5) or the anterior pelvic approach (4). X-rays (AP pelvic and AP hip) will be performed after 6 weeks, 4 months, 12 months, 5 and 10 years. Patients commence post-operative rehabilitation as usual until 4 months after the operation. Usual care means that the patients follow a rehabilitation program guided by a physiotherapist specialized in hip problems, with focus on stability and strength after the operation, as well as regaining a normal gait pattern. The physiotherapist will adapt the post-operative rehabilitation to the patients need and thus usual care will differ between patients." Four months postoperative the patients complete usual care and commence with the same PRT intervention program as the PRT group, until 12 months follow-up (see description above).

Protocol article version 8.11.19

METHOD

Training program

The PRT program involves 10-min of warm up followed by 4 exercises including sets of loaded squats, hip extension, hip flexion, and hip abduction. Loaded squat is performed standing with a barbell or dumbbells and target hip- and knee- extensors and flexors. Hip extension is performed standing in a cable-tower with a cable fixed around the ankle and the leg is moved backward and upward in a stretched position to perform hip-extension against resistance. Hip flexion is performed standing in a cable-tower with the cable fixed around the ankle and the knee is moved forward and upward to perform hip-flexion against resistance. Hip abduction is performed standing in a cable-tower with a cable fixed around the leg and leg is moved out to the side and up while kept stretched, to perform hip-abduction against resistance. To avoid muscle soreness of the affected leg (defined as index leg), squat is performed before the unilateral exercises. After week 16, all exercises are performed by both legs to train stability for the index leg and because the majority of the patients have bilateral hip dysplasia and hence probably profit from bilateral resistance training. The exercises are focused on strengthening all the muscles around the hip. Since patients with hip dysplasia primarily experience decreased strength in hip flexors and hip abductors (27), these muscles are incorporated in the training program, but to assure a symmetrical strengthening of the hip muscles, hip extensors are also included in the training program. Only 4 exercises have been included in the training program to ensure that the training sessions do not exceed 60 minutes, and consequently patients are more likely to adhere to the training program. The exercises are simple to perform, and all equipment used are standard equipment in essentially all fitness centres. The absolute training load will be individually adjusted on a set-by-set basis, using the plus two principle (if the patient is able to perform two or more repetitions than required, the load is increased). Hip related pain levels up to 5 on the VAS is considered acceptable during exercise (11). Progression of relative load will be performed as described in table 1.

Table 1.
Progressive resistance training descriptions over the 12 months intervention period

Exercise variable	Week 1-2	Week 3-4	Week 5-6	Week 7-52
Load	15 RM[b]	12 RM	10 RM	8 RM
Repetitions	10	12	10	8
Set per session	3	3	4	4
Rest between sets	90 sec.	90 sec.	120 sec.	120 sec.
Sessions per week	2	2	2	2
Duration of training period	52 weeks	52 weeks	52 weeks	52 weeks
Exercises	Loaded squat Hip extension Hip flexion Hip abduction	Loaded squat Hip extension Hip flexion Hip abduction	Loaded squat Hip extension Hip flexion Hip abduction	Loaded squat Hip extension Hip flexion Hip abduction
Contraction failure in each set	Yes	Yes	Yes	Yes
Range of motion	Maximal possible	Maximal possible	Maximal possible	Maximal possible
Rest between training sessions	>36 h	>36 h	>36 h	>36 h

After week 16, all exercises are performed by both legs. [b]Repetition Maximum (RM).

Outcomes

Outcome assessments will be performed at baseline, and at 4-months and 12-months follow-up (after initiation of surgical/non-surgical treatment). An assessor blinded to group allocation will conduct baseline and follow-up measurements. Five and 10 years after inclusion into the trial, the patients will be contacted and asked to complete hip-related questionnaires. An overview of the different outcomes is presented in Table 2.

Primary outcome:

The pain subscale of the patient-reported questionnaire HAGOS, were the total score ranges from 0 (worst) to 100 (best) (27). HAGOS is a valid, reliable, and responsive patient-reported outcome in young patients with hip and groin related pain (27). A minimal clinically relevant difference of the HAGOS pain subscale is considered to be 9.7 (28).

Secondary outcome:

The most important secondary outcomes are presented as key secondary outcomes. The key secondary outcomes are the other subscales of the HAGOS covering Symptoms, Physical function in daily living, Physical function in Sport and Recreation and Quality of Life; Single leg hop for distance (SLH) (29,30); adverse and serious adverse events (see Table 3) (31). Usage of painkillers (yes/no) and type of analgesics is also part of the key secondary outcomes. The other secondary outcomes are; HAGOS subscale Participation in Physical Activities; pain reported by the Visual Analogue Scale (VAS) (32); Forgotten joint score-12 (FJS-12) (33); Y-balance test (YBT) (34); and isometric measured hip muscle strength (flexion, extension and abduction).

Exploratory outcomes: Tri-axial accelerometer (only at baseline and 12-months follow-up); EuroQol Group 5-dimension self-report questionnaire with 5 levels (EQ-5D-5L) (35); delay to surgery and demographic differences between crossover patients compared to patients as treated in the PRT group.

Demographic data: Gender, age, height, weight, duration of hip symptoms, civil status, educational level, employment status, physical activity and exercise, alcohol intake, smoking behaviours and co-morbidities.

Assessment of compliance: Compliance to training will be registered from the patients' training protocols, described as number of sessions attended vs. number of planned sessions according to the protocol in per cent. Compliance to training will be calculated both for those who complete the intervention and for all patients, including drop-outs. High compliance is defined as ≥70% attendance to the supervised sessions the first 4 months. Number of self-training sessions will be recorded in a training diary and high compliance to self-training (from 4 to 12 months follow-up) is defined as attendance to the PRT of ≥50%.

X-rays: X-rays will be performed with the patient in standing position (AP pelvic) and in supine position (AP hip), at baseline and at every follow-up for both groups. X-rays will also be repeated at 6 weeks for the PAO-group as part of the standard postoperative care.

Data entry: In Denmark the software REDCap will be used for data entering, while EpiData will be used in Norway.

Protocol article version 8.11.19

Table 2.
Assessments and procedures

	Baseline	Surgery	4 months	12 months	5 years	10 years
Baseline characteristics						
Gender	X					
Age	X					
Height	X					
Weight	X		X	X		
Duration of hip symptoms	X					
Marital status	X					
Educational level	X					
Employment status	X					
Physical activity and exercise	X		X	X		
Alcohol intake	X					
Smoking behaviors	X					
Co-morbidities	X					
Patient-reported outcomes						
HAGOS[a]	X		X	X	X	X
EQ-5D-5L[b]	X		X	X	X	X
FJS-12[c]	X		X	X	X	X
Anchor questions			X	X		
Physical performance tests						
Single leg hop for distance	X		X	X		
Y-balance test	X		X	X		
Isometric hip muscle strength[d]	X		X	X		
Physical activity						
Tri-axial accelerometry	X			X		
Treatment related variables						
X-ray	X		X	X	X	X
Adverse events[e]			X	X		
Serious adverse events[e]			X	X		
Training-compliance			X	X		
Visual Analog scale[f]	X		X	X		
Other treatments			X	X		
Usage of analgesics	X		X	X		
Delay to surgery (only PRT-group)					X	X
Surgery (only PRT-group)			X	X	X	X

[a]The Copenhagen Hip and Groin Outcome Score (HAGOS). [b]European Quality of life 5 Dimensions with 5 Levels (EQ-5D-5L). [c]Forgotten Joint Score (FJS-12). [d]Isometric hip muscle strength: hip flexion, extension and abduction. [e]See Table 3. [f]VAS scores will be obtained before and after training.

Table 3.
Adverse and serious adverse events.

Adverse events
Haematoma
Delayed wound closure
Dysaethesia of lateral femoral cutaneous nerve
Malpositioning; retroversion or insufficient reorientation. Insufficient reorientation (coverage) – optimally is the CE angle 30-40 degrees and the AI angle 0-10 degrees.
Heterotopic ossifications (Brooker I and II)
Urinary tract infections
Infection not requiring surgical revision
Serious adverse events
Avascular necrosis of the femoral head or acetabulum
Nerve palsy
Major bleeding (administration of more than 5 blood units intra- and postoperatively)
Peroneal and femoral neurapraxia
Deep vein thrombosis
Pulmonary embolism
Stress fracture of ischial bone and posterior column
Intraarticular osteotomy
Heterotopic ossifications (Brooker III and IV)
Infection requiring surgical revision
Loss of fixation/loss of reorientation
Delayed or non-union of pubic, ischial or iliac bone

Anchor question

After 4 months, the patients will have an appointment with the surgeon. Before this meeting the patients will fill out the anchor question (described below) and the HAGOS questionnaire. These two questionnaires will form the basis of the talk with the surgeon. For patients allocated to the PRT group, the surgeon will ask the patient to evaluate to which extent the a priori hip problems have been addressed, and the patient and surgeon decide whether the patient continues in the PRT group they have been randomised to or is crossing-over to PAO. The decision of crossing-over is thus a decision made between the surgeon and the patient, based on the anchor question and the HAGOS questionnaire. After talking to the surgeon, function and muscle strength will be tested.

Anchor question

PAO-group: How is your operated hip now compared to before surgery? Much better, slightly better, the same, slightly worse or much worse?

PRT-group: How is your hip now compared to before you started this training program? Much better, slightly better, the same, slightly worse or much worse?

Sample size

A minimal clinically relevant difference of the HAGOS pain subscale is considered to be 9.7 (28). Based on a previous pilot trial the standard deviation of HAGOS pain in PAO patients is 16.2 (15). Given a power of 0.80 and two-sided significance level α=0.05, the estimated sample size of each intervention group is 44 patients. Allowing for possible crossovers and loss to follow-up, the number of included patients in each intervention group will be 48 patients.

Data availability statement

Aarhus University Hospital is responsible for handling all personal data provided by both sites in accordance to the Clinical Trial Agreement and the EU General Data Protection Regulation (GDPR). Oslo University Hospital agree that information directly related to the protocol and trial, including data, material, Intellectual Property and results generated from the trial shall be the property of Aarhus University Hospital, and shall be treated in strict confidence, and shall not be disclosed to any third party, or use for its benefit or the benefit of any third party, without the prior written consent of Aarhus University Hospital, except for data that is (i) publicly known or available from other sources who are not under a confidentially obligation to the other party; (li) has been made available by the other party without confidentiality obligation; or (iii) is independently developed or otherwise already known by or available to the other party without a confidentiality obligation; or (iv) is already required disclosed by law.

Statistical considerations

All descriptive statistics and tests will be reported in accordance with the recommendations of the *"Enhancing the QUAlity and Transparency Of health Research"* (EQUATOR) (36) network and the CONSORT statement (26). The primary efficacy analysis will be assessment of the between-group difference in change in the HAGOS pain subscale from baseline to 12 months after initiating the treatment (primary end-point). The primary analysis will follow the intention-to-treat principle and a mixed effects model will be used. Sensitivity and exploratory analysis will be performed with the purposes to test the robustness of the results per-protocol with good compliance (defined as participation in ≥70% of the training sessions) and as-treated analysis, in which patients will be analysed based on their adherence to the randomised treatment expecting three groups: (1) patients randomised to PAO, (2) patients randomised to PRT without undergoing PAO in the follow-up period, (3) patients randomised to PRT undergoing PAO in the follow-up period.

Ethics and dissemination

The trial is approved by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-234-18) and by the Danish Data Protection Agency (Journal No 1-16-02-120-19). The trial is also approved by The Regional Committee for Medical and Health Research Ethics, Region South-East Norway (Ref. 2018/1603). The trial is registered at Clinical Trial (NCT03941171). Before inclusion, all patients will have to give their written, informed consent in accordance with the Declaration of Helsinki II. All data and information collected in regard to this trial will be treated confidentially by the researchers and staff connected to the trial.

Patient and public involvement

During the development of the trial design, we have interviewed a group of patients with hip dysplasia with the purpose of gaining knowledge on the patients' thoughts on participating in a clinical trial that investigates the efficacy of joint preserving surgery compared to a PRT program. The patients were asked to consider how often they would be able to train, how far they would be willing to commute to the training facility and what their primary reason for seeking treatment had been. Likewise, they were asked about what was most important for them to achieve with an operation or a training intervention. This was performed in order to use the obtained knowledge to improve our patient information, the method of patient recruitment and the PRT program.

DISCUSSION

This is the first head-to-head comparison to evaluate the additive effect of PAO in addition to non-surgical treatment in patients with hip dysplasia scheduled for PAO. The trial will provide valuable evidence to surgeons, physiotherapists, and decision makers by highlighting the efficacy, benefits and harms of the surgical and non-surgical treatment approach, respectively. The results are expected to have an immediate substantial impact on clinical practise.

Since the trial is designed to be an assessor blinded randomised controlled trial, it reaches the highest evidence level. For obviously reasons it is not possible to blind the patients towards the intervention, which is a limitation of the trial. The trial is conducted at two University Hospitals and the patients are regular patients, thus the infrastructure used is of high standard. Both hospitals have specific hip units and have all necessary hospital equipment available including operational environment and post-operative hospitalization. All outcomes are valid and reliable outcome measures and consist of both multiple patient-reported outcomes and objective outcome measures.

There can be unforeseen risks in connection with all trials, but these are considered minimal in this trail. When performing PRT, it is normal to experience muscle soreness, and based on the experience from our earlier feasibility trial (15) testing PRT in patients with hip dysplasia, we know that there are times where the patients can experience muscle-related pain. The patients are thus asked to score their pain before and after each training session, to ensure that the training does not aggravate the hip pain. All methods included in this trial have been used in previous approved trials.

All results from the trial will be published in international peer-reviewed scientific journals regardless of whether the results are positive, negative or inconclusive.

Protocol article version 8.11.19

Author contributions

Lisa Reimer, Stig Jakobsen, Louise Mortensen, Ulrik Dalgas, Julie Jacobsen, Kjeld Søballe, Tone Bere, Jan Madsen, Lars Nordsletten, May Risberg and Inger Mechlenburg were a part of designing the trial and approved the final version of the protocol. Lisa Reimer and Inger Mechlenburg wrote the protocol and Stig Jakobsen, Louise Mortensen, Ulrik Dalgas, Julie Jacobsen, Kjeld Søballe, Tone Bere, Jan Madsen, Lars Nordsletten and May Risberg revised the protocol.

Data statement

After publishing, data regarding Danish patients will be stored at The Danish National Archives, while the data regarding Norwegian patients will be stored at The Norwegian National Archives. With the right approvals, data can be accessed there.

Funding

This trial is supported by Aarhus University (550,000 dkk), Aase and Ejnar Danielsens Foundation (84,000 dkk), Alfred Benzons Foundation (1,164,000 dkk), Andelsforeningernes Humanitære og Kulturelle Fond (20,000 dkk), Fondsstiftelsen ved Oslo Universitetssykehus (148.000 nok), The Danish Rheumatism Association (673,000 dkk), The Family Hede Nielsens Foundation (10,000 dkk), The Frimodt-Heineke Foundation (15,000 dkk) The Norwegian Fund for Post-Graduate Training in Physiotherapy (252.000 nok), The Riisfort Foundation (104,800 dkk) and Vanførefonden (100,000 dkk). The foundations had no role in planning the trial and did only deliver financial support.

Conflict of interest

None declared.

Ethics approval

The Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-234-18), the Danish Data Protection Agency (Journal No 1-16-02-120-19) and The Regional Committee for Medical and Health Research Ethics, Region South-East Norway (Ref. 2018/1603) approved the trial.

REFERENCES

1. Murphy SB, Ganz R, Muller ME. The prognosis in untreated dysplasia of the hip. A study of radiographic factors that predict the outcome. J Bone Jt Surgery Am Vol. 1995;77(7):985–9.
2. Jacobsen S, Sonne-Holm S. Hip dysplasia: a significant risk factor for the development of hip osteoarthritis. A cross-sectional survey. Rheumatology. 2005;44(2):211–8.
3. Wyles CC, Heidenreich MJ, Jeng J, Larson DR, Trousdale RT, Sierra RJ. The John Charnley Award: Redefining the Natural History of Osteoarthritis in Patients With Hip Dysplasia and Impingement. Clin Orthop Relat Res. 2017;475:336–50.
4. Ganz R, Klaue K, Vinh TS, Mast JW. A new periacetabular osteotomy for the treatment of hip dysplasias. Technique and preliminary results. Clin Prthop Relat Res. 1988;232:26–36.
5. Troelsen A, Elmengaard B, Soballe K. A new minimally invasive transsartorial approach for periacetabilar osteotomy. J Bone Jt Surgery Am Vol. 2008;90(3):493–8.
6. Steppacher SD, Tannast M, Ganz R, Siebenrock KA. Mean 20-year Followup of Bernese Periacetabular Osteotomy. Clin Orthop Relat Res. 2008;466(7):1633–44.
7. Lerch TD, Steppacher SD, Liechti EF, Tannast M, Siebenrock KA. One-third of Hips After Periacetabular Osteotomy Survive 30 Years With Good Clinical Results, No Progression of Arthritis, or Conversion to THA. Clin. 2017;475(4):1154–68.
8. Hartig-Andreasen C, Troelsen A, Thillemann TM, Søballe K, Hartvig-Andreasen C, Troelsen A, et al. What Factors Predict Failure 4 to 12 Years After Periacetabular Osteotomy? Clin Orthop Relat Res. 2012;470(11):2978–87.
9. Mechlenburg I, Nyengaard JR, Gelineck J, Soballe K. Cartilage Thickness and Cyst Volume Are Unchanged 10 Years After Periacetabular Osteotomy in Patients Without Hip Symptoms. Clin Orthop Relat Res. 2015;473(8):2644–9.
10. Mechlenburg I, Nyengaard JR, Rømer L, Søballe K. Changes in load-bearing area after Ganz periacetabular osteotomy evaluated by multislice CT scanning and stereology. Acta Orthop Scand. 2004;75(2):147–53.
11. Jacobsen S, Sonne-Holm S, Soballe K, Gebuhr P, Lund B. Joint space width in dysplasia of the hip: a case-control study of 81 adults followed for ten years. J Bone Jt Surg. 2005;87(4):471–7.
12. Morita D, Hasegawa Y, Seki T, Amano T, Takegami Y, Kasai T, et al. A Possible New Radiographic Predictor of Progression of Osteoarthritis in Developmental Dysplasia of the Hip: The Center Gap. Clin Orthop Relat Res. 2018;476(11):2157–66.
13. Troelsen A, Romer L, Soballe K. [Hip dysplasia: clinical assessment, radiologic evaluation and reference]. Ugeskr Laeger. 2007;169(5):394–6.
14. Sørensen H, Nielsen DB, Jacobsen JS, Søballe K, Mechlenburg I. Isokinetic dynamometry and gait analysis reveal different hip joint status in patients with hip dysplasia. HIP Int. 2019;29(2):215–21.
15. Mortensen L, Schultz J, Elsner A, Jakobsen SS, Søballe K, Jacobsen JS, et al. Progressive resistance training in patients with hip dysplasia: A feasibility study. J Rehabil Med. 2018;50(8):751–8.
16. Clohisy JC, Nepple JJ, Ross JR, Pashos G, Schoenecker PL. Does Surgical Hip Dislocation and Periacetabular Osteotomy Improve Pain in Datients with Perthes-like deformities and Acetabular Dysplasia? Clin Orthop Relat Res. 2015;473(4):1370–7.
17. Kanai A, Kiyama T, Genda E, Suzuki Y. Biomechanical investigation of ambulatory training in patients with acetabular dysplasia. Gait Posture. 2008;28(1):52–7.

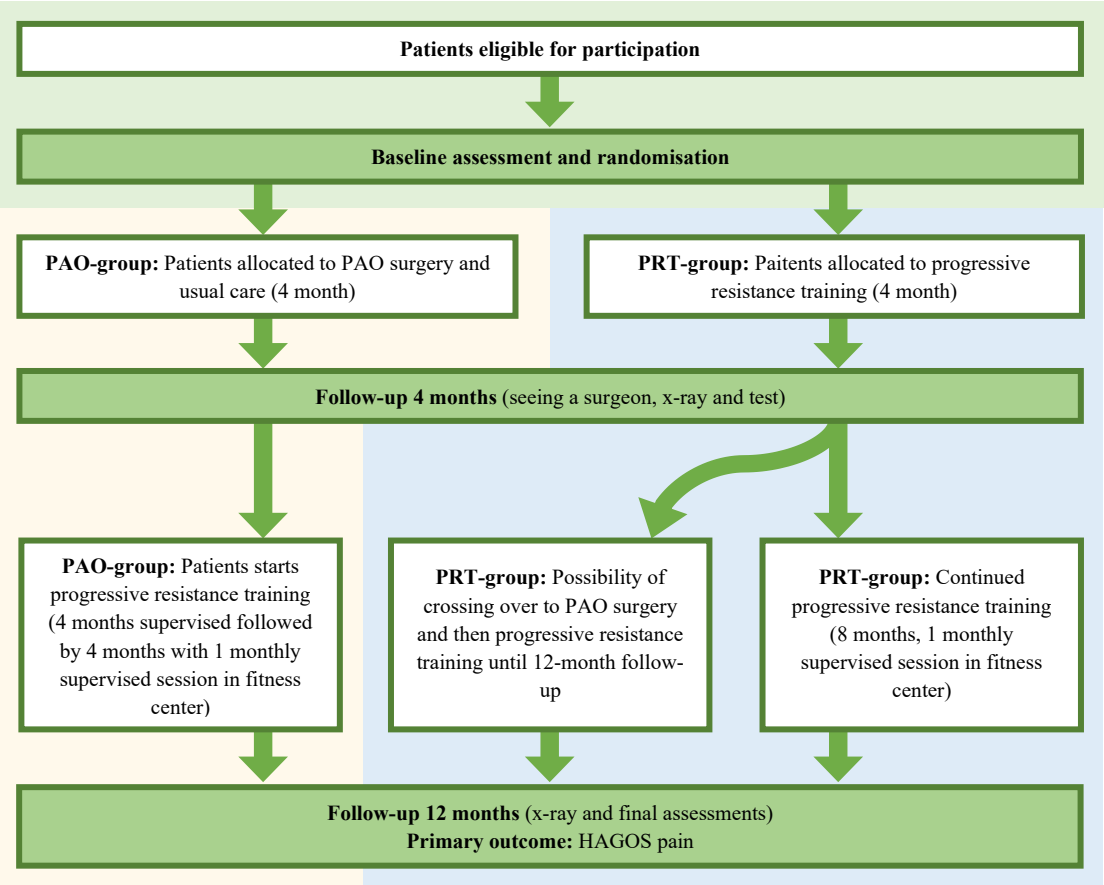
18. Kuroda D, Maeyama A, Naito M, Moriyama S, Yoshimura I, Nakamura Y, et al. Dynamic hip stability, strength and pain before and after hip abductor strengthening exercises for patients with dysplastic hips. Isokinet Exerc Sci. 2013;21(2):95–100.
19. Harris-Hayes M, Czuppon S, Van Dillen LR, Steger-May K, Sahrmann S, Schootman M, et al. Movement Pattern Training To Improve Function in People with Chronic Hip Joint Pain: A Feasibility Randomized Clinic Trial. J Orthop Sport Phys Ther. 2016;46(6):452–61.
20. Bieler T, Siersma V, Magnusson SP, Kjaer M, Christensen HE, Beyer N. In hip osteoarthritis, Nordic Walking is superior to strength training and home-based exercise for improving function. Scand J Med Sci Sport. 2017;27(8):873–86.
21. Hermann A, Holsgaard-Larsen A, Zerahn B, Mejdahl S, Overgaard S. Preoperative progressive explosive-type resistance training is feasible and effective in patients with hip osteoarthritis scheduled for total hip arthroplasty - a randomized controlled trial. Osteoarthr Cartil. 2016;24(1):91–8.
22. Wartolowska K, Judge A, Hopewell S, Collins GS, Dean BJF, Rombach I, et al. Use of placebo controls in the evaluation of surgery: systematic review. BMJ [Internet]. 2014;348:g3253. Available from: http://dx.doi.org/doi:10.1136/bmj.g3253
23. Wartolowska K, Beard DJ, Carr AJ. Attitudes and Beliefs about Placebo Surgery among Orthopedic Shoulder Surgeons in the United Kingdom. PLoS One. 2014;9(3):e91699.
24. Zurmuhle CA, Anwander H, Albers CE, Hanke MS, Steppacher SD, Siebenrock KA, et al. Periacetabular Osteotomy Provides Higher Survivorship Than Rim Trimming for Acetabular Retroversion. Clin Orthop Relat Res. 2017;475(4):1138–50.
25. Belzile EL, Beaule PE, Ryu J-J, Clohisy JC. Outcomes of joint preservation surgery: comparison of patients with developmental dysplasia of the hip and femoroacetabular impingement. J Hip Preserv Surg. 2016;3(4):270–7.
26. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010;63(8):e1–37.
27. Thorborg K, Holmich P, Christensen R, Petersen J, Roos EM, Hölmich P, et al. The Copenhagen Hip and Groin Outcome Score (HAGOS): development and validation according to the COSMIN checklist. Br J Sport Med. 2011;45(6):478–91.
28. Thomeé R, Jónasson P, Thorborg K, Sansone M, Ahldén M, Thomeé C, et al. Cross-cultural adaptation to Swedish and validation of the Copenhagen Hip and Groin Outcome Score (HAGOS) for pain, symptoms and physical function in patients with hip and groin disability due to femoro-acetabular impingement. Knee Surg Sport Traumatol Arthrosc. 2014;22(4):835–42.
29. Ageberg E, Cronström A. Agreement between test procedures for the single-leg hop for distance and the single-leg mini squat as measures of lower extremity function. BMC Sports Sci Med Rehabil. 2018;10:15:1–7.
30. Kemp JL, Risberg MA, Schache AG, Makdissi M, Pritchard MG, Crossley KM. Patients With Chondrolabral Pathology Have Bilateral Functional Impairments 12 to 24 Months After Unilateral Hip Arthroscopy: A Cross-sectional Study. J Orthop Sport Phys Ther. 2016;46(11):947–56.
31. Biedermann R, Donnan L, Gabriel A, Wachter R, Krismer M, Behensky H. Complications and patient satisfaction after periacetabular pelvic osteotomy. Int Orthop. 2008;32(5):611–7.
32. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire

(MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. Arthritis Care Res. 2011;63(SUPPL. 11):S240–52.
33. Behrend H, Giesinger K, Giesinger JM, Kuster MS. The "Forgotten Joint" as the Ultimate Goal in Joint Arthroplasty. Validation of a New Patient-Reported Outcome Measure. J Arthroplasty. 2012;27(3):430-436.e1.
34. Plisky PJ, Gorman PP, Butler RJ, Kiesel KB, Underwood FB, Elkins B. The reliability of an instrumented device for measuring components of the star excursion balance test. North Am J Sport Phys Ther. 2009;4(2):92–9.
35. Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727–36.
36. Christensen R, Bliddal H, Henriksen M. Enhancing the reporting and transparency of rheumatology research: A guide to reporting guidelines. Arthritis Res Ther. 2013;15(1):1–4.

Protocol article version 8.11.19

Figure legend:

Figure 1. Patient flow through the trial



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	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
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 + 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	14
Roles and responsibilities: committees	#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)	4
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	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
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, non-inferiority, exploratory)	4
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	4

		collected. Reference to where list of study sites can be obtained	
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)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-6
Interventions: modifications	#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)	5 + 12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
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	8-11
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)	7
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	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	4

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	5
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	5
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#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 plan	#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	7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for	n/a

		participants who discontinue or deviate from intervention protocols	
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	9
Statistics: outcomes	#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	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
Statistics: analysis population and missing data	#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)	12
Methods: Monitoring			
Data monitoring: formal committee	#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. No monitoring in this study
Data monitoring: interim analysis	#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. No monitoring in this study
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	7
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a. No auditing in this study
Ethics and dissemination			

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
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)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
Consent or assent: ancillary studies	#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	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
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	n/a
Dissemination policy: trial results	#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	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a

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

Notes:

- 21a: n/a. No monitoring in this study
- 21b: n/a. No monitoring in this study
- 23: n/a. No auditing in this study This checklist was completed on 05. July 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai