

# BMJ Open Progressive resistance training compared to neuromuscular exercise in patients with hip osteoarthritis and the additive effect of exercise booster sessions: protocol for a multicentre cluster randomised controlled trial (The Hip Booster Trial)

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## ABSTRACT

**Introduction** The primary aim of this randomised controlled trial is to investigate the effectiveness of 3 months of progressive resistance training (PRT) compared to neuromuscular exercise (NEMEX) on functional performance in patients with hip osteoarthritis (OA). Secondary aims are to investigate the effectiveness of exercise booster sessions (EBS) in prolonging the effects of the initial exercise interventions as well as to investigate the cost-effectiveness of PRT, NEMEX and EBS at 12-month follow-up.

**Methods and analysis** This multicentre cluster randomised controlled trial will be conducted at hospitals and physiotherapy clinics across Denmark. A total of 160 participants with clinically diagnosed hip OA will be recruited. Participants will be cluster randomised to a 3-month intervention of either PRT or NEMEX and to receive EBS or not, resulting in four treatment arms. The primary outcome is change in functional performance, measured by the 30s chair stand test at 3 months for the primary comparison and at 12 months for the EBS comparisons. Secondary outcomes include changes in 40 m fast-paced walk test, 9-step timed stair climb test, leg extensor muscle power and maximal strength, Hip disability and Osteoarthritis Outcome Score subscales, EuroQol Group 5-dimension, global perceived effect, physical activity and pain. Outcomes are measured at baseline, after the initial 3 months of intervention, and at 6-month, 9-month and 12-month follow-up. An intention-to-treat approach will be used for analysing changes in the primary and secondary outcome measures.

**Ethics and dissemination** The trial has been approved by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-267-20) and registered at the Danish Data Protection Agency (Journal No 1-16-02-11-21). Results will be published in international peer-reviewed scientific journals.

**Trial registration number** NCT04714047.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a cluster randomised, controlled, assessor-blinded, parallel-group trial providing high-quality evidence on exercise therapy for hip osteoarthritis.
- ⇒ This pragmatic multicentre trial is carried out at several hospitals and physiotherapy clinics across Denmark increasing the feasibility of subsequent implementation of the interventions.
- ⇒ The primary outcome is an objective test of functional performance and is less susceptible to performance bias compared with subjective measures.
- ⇒ The physiotherapists and patients will not be blinded to treatment allocation, which may introduce bias.
- ⇒ We are not able to distinguish between the specific treatment effects and the contextual effects of the interventions.

## INTRODUCTION

Osteoarthritis (OA) is the most common joint disease and a leading cause of disability worldwide.<sup>1</sup> OA is becoming more prevalent in the ageing and increasingly obese population, placing a substantial burden on health-care systems and causing large societal costs.<sup>2</sup>

Exercise is a safe, feasible and effective treatment for patients with hip OA, reducing pain and improving physical function, and is strongly recommended by professional societies.<sup>3-6</sup> Content and dosage of exercise interventions seem to be important for the magnitude of the effects.<sup>7</sup> However, different exercise modalities in hip OA have only sparsely been compared<sup>8,9</sup> and exercise recommendations suggesting one type of exercise over another are not based on solid

evidence.<sup>5</sup> The most recent Cochrane review concluded that there is a need for ‘multiarmed randomised controlled trials to help provide evidence of optimal exercise content and dosage’.<sup>6</sup>

Neuromuscular exercise (NEMEX) has been shown to improve physical function and alleviate symptoms in patients with hip OA.<sup>10–13</sup> A few trials on progressive resistance training (PRT) in hip OA suggest positive effects on pain, physical function and quality of life.<sup>8 14–16</sup> The frequently observed muscle atrophy and weakness in patients with hip OA offer a rationale for PRT,<sup>17</sup> since PRT is generally considered the most potent intervention to increase muscle mass and strength.<sup>18</sup> Hence, PRT may be superior to NEMEX in improving functional performance and pain in patients with hip OA. Consequently, a head-to-head study comparing these two exercise modalities in patients with hip OA is warranted.

One major challenge related to exercise interventions in hip OA is that effects are typically not maintained in the long term.<sup>19 20</sup> Importantly, higher adherence to a post-treatment home exercise programme was associated with better long-term treatment effects.<sup>21</sup> This warrants research in interventions aimed at improving long-term exercise adherence and thereby prolonging the initial effects. One such intervention is exercise booster sessions (EBS), which is training sessions provided regularly throughout the follow-up period to sustain effects of the preceding exercise intervention and to motivate participants to continue exercising after the initial supervised training sessions have ended.<sup>22</sup> In knee OA, there is some evidence to suggest that EBS may improve pain and self-reported disability<sup>23</sup> and lead to cost savings for the healthcare system.<sup>24</sup> Prior studies investigating EBS in patients with hip OA did not provide treatment arms with an identical initial exercise intervention, and thus, cannot determine the effectiveness of EBS for maintaining the effects of an initial intervention.<sup>22 25–28</sup> This highlights the need for trials investigating the effectiveness of EBS compared with a control group receiving no EBS in patients with hip OA.

## AIM AND HYPOTHESES

The primary aim of this trial is to investigate the effectiveness of 3 months of PRT compared with NEMEX on functional performance in patients with hip OA. Secondary aims are to investigate the effectiveness of EBS in prolonging the effects of the initial exercise interventions as well as to investigate the cost-effectiveness of PRT, NEMEX and EBS.

The primary hypothesis for the 3-month comparison is that PRT is superior to NEMEX in improving functional performance, measured by the 30 s chair stand test (CST). The primary hypothesis for the 12-month comparison is that EBS are superior to no EBS in improving functional performance, measured by the 30 s CST, regardless of allocation to PRT or NEMEX. Secondary hypotheses for the 12-month comparisons are that: (1)

EBS is cost-effective compared with no EBS; (2) PRT is cost-effective compared with NEMEX regardless of allocation to EBS or no EBS; (3) PRT with EBS is cost-effective compared with PRT without EBS and NEMEX with EBS is cost-effective compared with NEMEX without EBS; (4) PRT followed by EBS is superior to PRT without EBS, and that NEMEX followed by EBS is superior to NEMEX without EBS in improving functional performance, measured by the 30 s CST and (5) PRT is superior to NEMEX in improving functional performance, measured by the 30 s CST regardless of allocation to EBS.

## METHODS AND ANALYSIS

### Study design

This multicentre, cluster randomised, controlled, parallel-group, assessor-blinded, superiority trial will be conducted at 5 hospitals and 10 physiotherapy clinics across Denmark. Following the baseline test, participants will be cluster randomised to a 3-month intervention of either PRT or NEMEX and additionally to receive EBS or not, resulting in four treatment arms (see [figure 1](#)). EBS will be provided at 1, 3, 5 and 7 months after conclusion of the initial intervention. After baseline testing, the intervention is started as soon as possible. The primary outcome is change in functional performance, measured by the 30 s CST, and the primary endpoint is at 3 months after starting the intervention for the comparison between PRT and NEMEX and at 12 months for the comparison of EBS and no EBS. Secondary outcomes will be measured at baseline, and at 3-month, 6-month, 9-month and 12-month follow-up.

This protocol is written in accordance with the SPIRIT guideline<sup>29</sup> and the interventions are described according to the CERT guidelines<sup>30</sup> and the mechanobiological determinants suggested by Toigo and Boutellier.<sup>31</sup> The results of this trial will be reported following the CONSORT statement guidelines.<sup>32</sup>

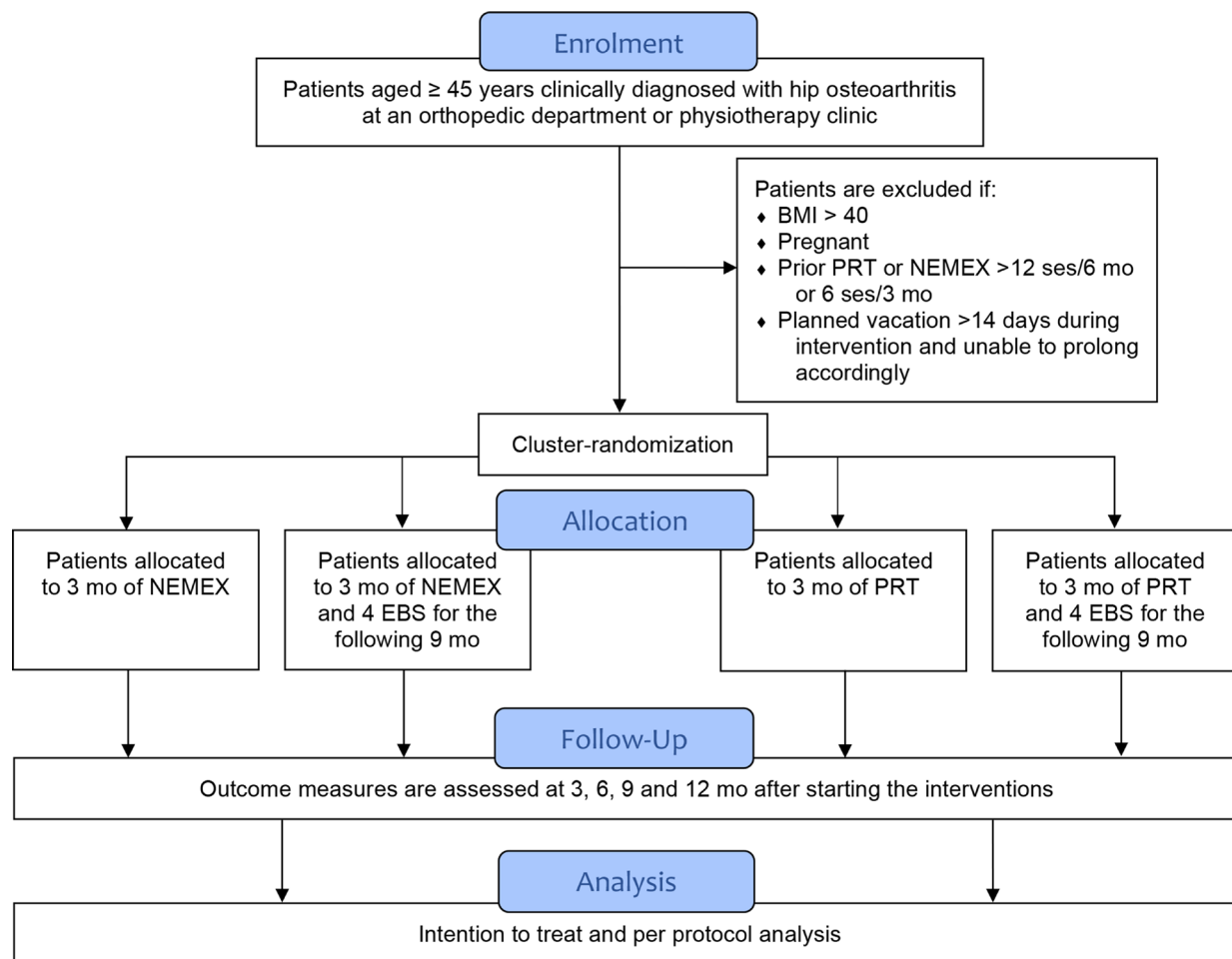
Participant enrolment started on January 2021 and is expected to be completed by October 2022. All participants are expected to have completed 12-month follow-up assessments by December 2023, marking the end of the study.

### Participants

Participants will be recruited from 4 of the 5 hospitals and 10 physiotherapy clinics across three healthcare regions of Denmark. Participants are initially screened and given participant information verbally and in writing. After 24 hours, they are contacted by an assessor, with an invitation to baseline assessment. Before the baseline assessment participants give written informed consent.

### Inclusion criteria

(1) Clinically diagnosed OA of the hip joint according to the National Institute for Health and Care Excellence criteria;<sup>33</sup> (2) An event of pain during activity of at least 3 out of 10 on a Numerical Rating Scale (NRS) in the index



**Figure 1** CONSORT (CONSolidated Standards Of Reporting Trials) flow chart describing the study design. BMI, body mass index; EBS; exercise booster sessions; NEMEX; neuromuscular exercise; PRT; progressive resistance training; SES; exercise sessions.

hip within the last 2 weeks; (3) Age  $\geq 45$  years; (4) No hip joint morning stiffness or less than 30 min; (5) No surgery in the lower extremities 6 months prior to inclusion; (6) No comorbidity that markedly affects hip function; (7) Adequacy in written and spoken Danish and (8) Not being a candidate for total hip arthroplasty.

#### Exclusion criteria

(1) Body mass index score  $> 40$ ; (2) Pregnancy; (3) PRT or NEMEX for the lower extremities exceeding 12 sessions over the last 6 months or 6 sessions over the last 3 months and (4) Planned vacation for more than 14 days within the initial 3-month intervention period without the possibility of prolonging the intervention accordingly.

#### Randomisation and treatment allocation

After recruitment and baseline assessment, participants will be randomised to either PRT, NEMEX, PRT+B or NEMEX+B by cluster randomisation stratified by recruitment site according to a randomly generated sequence of numbers. A member of the research team (IM) who is not involved in recruitment, assessment or treatment, generated the allocation sequence for each of the 14 sites by drawing tokens from a bag containing an even distribution

of the four allocations. The sequence will be concealed to the physiotherapists who enrol participants. The cluster size is set at five participants and each cluster forms an exercise group that will attend group sessions together. However, to keep the waiting time at an acceptable level, groups of 1–4 participants are cluster randomised if they have waited  $> 14$  days after inclusion. Cluster randomisation was chosen to allow timely formation of the exercise groups and to avoid treatment contamination between interventions.

#### Blinding

Outcome assessors will conduct baseline and follow-up assessment blinded to group allocation. Prior to the 3-month and 12-month assessment, participants will be instructed not to disclose the allocated treatment. The participants and the physiotherapists delivering the exercise interventions will not be blinded to group allocation.

#### Interventions

The exercise interventions will be performed at the collaborating hospitals and physiotherapy clinics. All sessions will be conducted as group sessions with one physiotherapist supervising the exercises. Each cluster

**Table 1** Descriptors of the progressive resistance training and neuromuscular exercise interventions

Exercise type	Progressive resistance training			Neuromuscular exercise
	Block 1 (Weeks 1–4)	Block 2 (Weeks 5–8)	Block 3 (Weeks 9–12)	
Periodisation model				Exercise difficulty level is progressed linearly throughout the intervention
Volume (rep/set)	12	10	8	10 to 15
Exercise intensity	12 RM	10 RM	8 RM	Not controlled for
Sets/exercise (n)	3			2 to 3
Muscle contraction types				Every contraction phase is performed with maximal control, functional alignment and a steady pace (1 to 3s)
Concentric	As fast as possible			
Isometric	1 s			
Eccentric	3 s			
Time under tension (s/rep)	4–6			Not controlled for
Time between repetitions (s)	0			0
Time between sets (s)	60			Equivalent to completing one set
Session duration (m)	60			60
Sessions/week (n)	2			2
Time between sessions (h)	>72			>72
Supervised and group based	Initial 12 weeks			Initial 12 weeks
Focus for exercises	Maximal intensity (exercise weight) and volume without compromising technique			Stability, postural function, postural orientation, lower extremity muscle strength, functional exercises
Range of motion	Full			Full
Volitional muscle failure	Third set only			Not controlled for
Order of adjusting exercises in case of pain exacerbation	Pace → range of motion → intensity			Pace → range of motion → no of repetitions → difficulty level
Progression	When able to perform all assigned repetitions in the third set, the weight is increased by 2%–10%			When able to perform 15 repetitions for three sets with good sensorimotor control, movement quality and acceptable exertion, progression is made to the next level of difficulty.
Equipment	Leg press machine, knee extension machine, hyperextension bench, dumbbells, cable pulley, ankle straps			Aerobic stepper, pilates exercise ball, elastic bands, sliding mat, chair with armrest, foam balance pad

h, hours; m, minutes; n, number; rep, repetitions; RM, repetition maximum; ROM, range of motion; s, seconds; w, weeks.

will be supervised once by the principal investigator, to further ensure fidelity to the protocol. The duration and frequency of the interventions will be 3 months with two supervised sessions each week interspersed by 72 hours. This results in 24 sessions, each lasting 60 min. Each session consists of a 10 min submaximal warm-up on an exercise bike at an intensity of 13–14 on Borgs Rating of Perceived Exertion scale,<sup>34</sup> followed by 50 min of PRT or NEMEX. If participants experience pain during exercise exceeding 5 out of 10 on an NRS, the physiotherapist will modify the exercise, decreasing the exercise intensity (load), modifying the range of motion or changing the tempo of the exercise. All unilateral exercises will be performed for both legs. During the exercise interventions, the physiotherapists informed the patients on pain flares, pain management and that exercising with OA is safe. There are no restrictions for concomitant care.

#### Neuromuscular exercise

The NEMEX intervention (described in [table 1](#) and [figure 2](#)) will follow the programme as described by

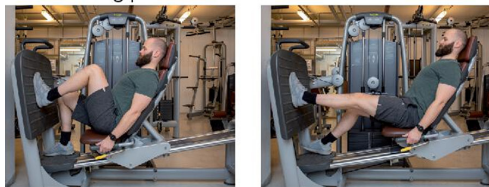
Ageberg *et al*<sup>12</sup> with the exception that the 10 min cool-down is left out. Ten exercises are performed each session and progression is primarily provided by four levels of difficulty and second by varying the number of, direction, and velocity of the movements and/or changing the support surface.<sup>12 35</sup> At the first session, the physiotherapist assesses each participant to determine at which level the participant will start. The exercises are tailored to the individual to improve movement quality, reduce pain or increase the difficulty of the movement.

#### Progressive resistance training

The PRT intervention (described in [table 1](#) and [figure 2](#)) consists of five generic exercises that are performed each session, targeting the muscles of the hip and knee joints. The progression will follow linear periodisation in line with guidelines by the American College of Sports Medicine.<sup>36 37</sup> For the first session, the physiotherapist will estimate an exercise intensity of 50% of 1-repetition maximum (RM) for each

## Progressive resistance training

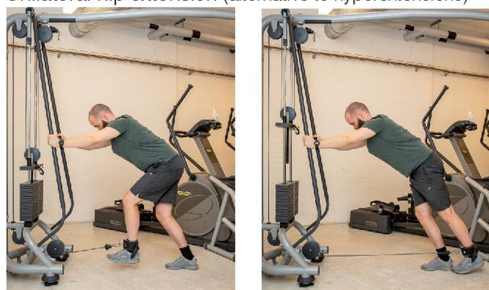
### Unilateral leg press



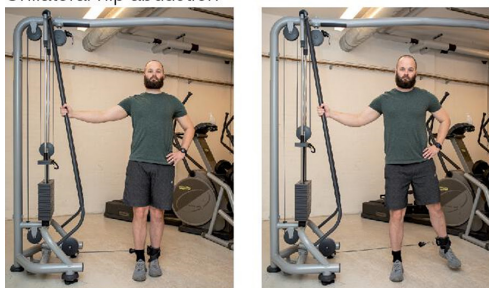
### Hyperextensions



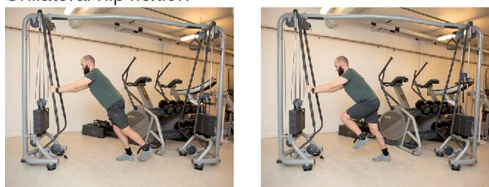
### Unilateral hip extension (alternative to hyperextensions)



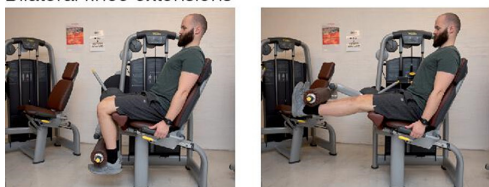
### Unilateral hip abduction



### Unilateral hip flexion



### Bilateral knee extensions



## Neuromuscular exercise (difficulty 4)

### Pelvic lift



### Sit ups



### Slide-exercise forw.-backw.



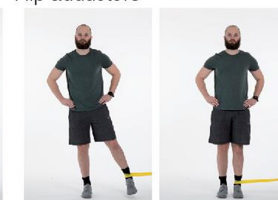
### Slide-exercise sideways



### Hip abductors



### Hip adductors



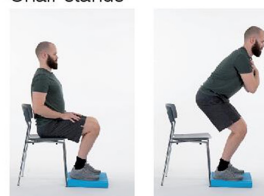
### Knee extensors



### Knee flexors



### Chair stands



### Stair climbing



**Figure 2** Exercises at starting position (left) and at end-range of motion (right) for the two exercise interventions. Only difficulty level 4 is shown for the neuromuscular exercises while level 1–3 can be found as an additional file to the article by Ageberg *et al.*<sup>12</sup>

exercise. In every third set, participants are instructed to continue performing the exercise until volitional muscular failure. If a participant reaches the RM target repetitions or more for the third set, the exercise intensity (weight) will be increased by 2%–10% depending on the level of exertion.

### Self-administered exercise and EBS

After the initial 3-month interventions, participants in all four groups are given a training programme and encouraged to continue performing the same exercises independently twice weekly through the 9-month follow-up period, starting at the level they reached during the initial

intervention. The NEMEX and NEMEX+B groups will be provided with the equipment for NEMEX in their home (one aerobic stepper, one pilates exercise ball and two elastic bands). The PRT and PRT+B groups will be offered a membership to a training facility. The facility staff will be told not to give any supervision to the study participants. The EBS groups (PRT+B and NEMEX+B) will receive four EBS provided at 1, 3, 5 and 7 months after the initial interventions. At each EBS, the participants are performing an as-usual group-based training session while the physiotherapist reviews the self-administered programmes following a standardised screening of potential complications and provides recommendations for modification of the programmes.

### Outcomes measures

All outcome measures will be assessed at the participating hospital departments at baseline, within 1 week after the end of the 3-month group-based intervention, and at 12-month follow-up (see [table 2](#)). The EuroQol Group 5-dimension (EQ-5D-5L), iMTA Productivity Costs Questionnaire (IPCQ) and Health Utilisation Questionnaire (HUQ) will additionally be assessed at 6-month and 9-month follow-up. The outcome assessors are physiotherapists, who are trained in performing the assessments according to a standardised protocol.

### Participant characteristics

The following information will be obtained from the participants at baseline: gender, age, height, weight (also at three and 12 months), civil status, educational level, employment status, substance use (alcohol and smoking), duration of symptoms, index hip, previous treatment, pain medication, joint replacements (also at 12 months), and other diseases.

### Primary outcome

#### *Thirty-second chair stand test*

The 30 s CST is a valid and responsive measure with excellent reliability evaluating sit-to-stand function (number of repetitions).<sup>38–40</sup> The 30 s CST was chosen as the primary outcome because it is an objective measure of functional performance (low risk of performance bias) that is easily standardised between test locations while sit-to-stand function is affected in people with hip OA<sup>41 42</sup> negatively impacting activities of daily living.<sup>43</sup> Identical chairs (44 cm seat height, no armrest) are provided for each test location.

### Key secondary outcomes

#### *Hip disability and Osteoarthritis Outcomes Score*

The Hip disability and Osteoarthritis Outcomes Score (HOOS) is a 40-item patient-reported questionnaire consisting of five subscales. Each subscale gives a score ranging from 0 (worst) to 100 (best).<sup>44</sup> HOOS is a valid, reliable and responsive measure in patients with hip OA.<sup>45</sup> The pain and hip-related quality of life subscales are chosen as key secondary outcomes and will help guide the conclusion.

**Table 2** Outcome measures and corresponding instruments and time points for data collection

Outcome	Instrument	Time points
<b>Functional tests</b>		
Sit-to-stand function (PO)	30 s chair stand test	B, 3 and 12 months
Maximum walking speed	40 m fast-paced walk test	B, 3 and 12 months
Stair negotiation	9-step timed stair climb test	B, 3 and 12 months
Leg extensor muscle power	Nottingham Power Rig	B, 3 and 12 months
Leg extensor muscle strength	Unilateral 1RM leg press test	B, 3 and 12 months
<b>Patient-reported outcomes</b>		
Health-related QoL	Questionnaire (EQ-5D-5L)	B, 3, 6, 9 and 12 months
Health utilisation	Questionnaire (HUQ)	B, 3, 6, 9 and 12 months
Productivity losses	Questionnaire (IPCQ)	3, 6, 9 and 12 months
Symptoms	Questionnaire (HOOS)	B, 3 and 12 months
Pain	Questionnaire (HOOS), NRS	B, 3 and 12 months
ADL function	Questionnaire (HOOS)	B, 3 and 12 months
Sport/recreation	Questionnaire (HOOS)	B, 3 and 12 months
Hip-related QoL	Questionnaire (HOOS)	B, 3 and 12 months
Global perceived effect	Questionnaire (GPE)	3 and 12 months
Physical activity	Questionnaire (SNBHW)	B, 3 and 12 months
THA (yes/no)	Questionnaire	B and 12 months
<b>Patient characteristics</b>		
Sex	Questionnaire	B
Age	Questionnaire	B
Height	Questionnaire	B
Weight	Questionnaire	B, 3 and 12 months
Civil status	Questionnaire	B
Educational level	Questionnaire	B
Employment status	Questionnaire	B
Substance use	Questionnaire	B
Duration of symptoms	Questionnaire	B
Index hip	Questionnaire	B
Previous treatment	Questionnaire	B
Pain medication	Questionnaire	B
Other diseases	Questionnaire	B
<b>Treatment-related variables</b>		
Adverse events	Supervision and questionnaire	Throughout study period

Continued

**Table 2** Continued

Outcome	Instrument	Time points
Adherence to interventions	Supervision	Training sessions
Pain during exercise	NRS	Before and after each training session
Drop-outs	Supervision	Throughout study period
Lost to follow-up	Supervision	Throughout study period

3 and 12 months, follow-up test sessions 3 and 12 months after starting the intervention; B, baseline test; EQ-5D-5L, EuroQol Group 5-dimension; GPE, Global perceived effect; HOOS, Hip disability and Osteoarthritis Outcomes Score; HUQ, Health Utilisation Questionnaire; IPCQ, Productivity Costs Questionnaire; NRS, Numeric Rating Scale; PO, primary outcome; QoL, quality of life; 1RM, one-repetition-maximum; SNBHW, The Swedish National Board of Health and Welfare questionnaire; THA, total hip arthroplasty.

## Secondary outcomes

### *Hip disability and Osteoarthritis Outcomes Score*

The HOOS subscales for symptoms, activities of daily life function and sport/recreation are secondary outcome measures.<sup>44</sup>

### *Forty metre fast-paced walk test*

The 40 m fast-paced walk test measures the total time (in seconds) it takes to walk 4×10 m (s) excluding turns. It is a valid and responsive measure of short distance maximum walking speed with excellent reliability.<sup>46</sup>

### *Nine-step timed stair climb test*

The 9-step timed stair climb test measures the time (in seconds) spent to ascend and descend nine steps and has excellent reliability in patients with symptomatic hip OA.<sup>47</sup>

### *Nottingham leg extensor power rig*

Leg extensor muscle power (watt/kg) will be measured using the Nottingham Power Rig, which has excellent reliability in patients with symptomatic hip OA.<sup>47 48</sup> Leg extensor muscle power is a clinically important measure strongly correlated to physical function.<sup>49</sup> For each leg, participants perform two warm-up trials followed by at least five trials with 30 s rest between trials, until the participant does not improve in two successive trials, or at a maximum of 10 trials.

### *Unilateral one-repetition-maximum leg press*

Maximal leg extensor strength of the index hip is measured by a 1RM test in a leg press resistance training machine, which is a highly reliable test in elderly populations.<sup>50</sup> Warm-up consists of a set of 10 repetitions against a weight equivalent to 50% bodyweight. The weight for the first 1RM attempt is set corresponding to the rate of exertion during the warm-up set and the best result is found within five 1RM attempts.

### *Global perceived effect*

The global perceived effect (GPE) will be assessed for three domains; pain, activities of daily living and quality of life, on a 7-point Likert scale.<sup>51</sup>

### *Adverse events and serious adverse events*

Throughout the trial, there will be continuous registration of adverse events (AE) and serious AEs (SAEs) as defined by The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.<sup>52</sup> Physiotherapists supervising the exercise sessions will monitor events. During the 3-month and 12-month follow-up, the participants will be asked about potential AE and SAE using open-probe questions to be reported according to recommendations given by the CONSORT Group.<sup>32</sup> SAEs will be reported to the Central Denmark Region Committee on Biomedical Research Ethics. In case of an unexpected high rate of AE and SAE in either group, the project group will consider study termination.

### *Adherence and drop-outs*

Adherence to training will be registered by the physiotherapists supervising the exercise sessions. High adherence for the initial 3 months is defined as ≥80% attendance to the supervised exercise sessions. High adherence for the 9 months self-administered exercise is defined as ≥80% completion of the self-managed exercise sessions. Number of drop-outs and lost to follow-up will be registered throughout the study.

## Other outcomes

### *Physical activity*

Physical activity and sedentary behaviour are measured by The Swedish National Board of Health and Welfare questionnaire, which is a three-domain categorical answer patient-reported questionnaire.<sup>53</sup>

### *Numerical rating scale for pain*

Pain intensity is measured on a 11-item NRS where 0 represents no pain and 10 represent the worst pain imaginable.<sup>54</sup>

### *Societal costs*

Health utilisation is measured by a nine-item patient-reported cost questionnaire (HUQ) assessing healthcare and medicine usage.<sup>55</sup> Productivity losses of paid work due to absenteeism, presenteeism and losses related to unpaid work is measured by the IPCQ.<sup>56</sup>

### *EuroQol Group 5-dimension*

The EQ-5D-5L is a patient-reported, valid and reliable questionnaire in patients with hip OA assessing health-related quality of life. The EQ-5D-5L measures the five dimensions: mobility, self-care, daily activities, pain/discomfort and anxiety/depression. Each dimension consists of one item, distinguished in five levels (no, slight, moderate, severe problems, unable to do). The EQ-5D also includes a visual analogue scale on which the

patients rate their health on a scale from 0 (worst imaginable health) to 100 (best imaginable health).<sup>57 58</sup>

### Data management

The project is registered at the Danish Data Protection Agency (Journal No 1-16-02-11-21). Before inclusion, all participants will have to give their written, informed consent in accordance with the Declaration of Helsinki II. All data collected in this trial is directly entered into the Research Electronic Data Capture (REDCap) for safe storage and will be treated confidentially by the research staff. The patient-reported data is entered into the REDCap database by the patient. Questionnaires are sent by email to participants at 6 months and 9 months follow-up. No data monitoring committee was established.

### Sample size

The sample size calculation is based on the expected between-group difference in the 30 s CST from baseline to 3-month follow-up. Due to lack of hip OA specific data, the sample size calculation relies on data from knee OA. A mean change of 2.5 chair stands was found by Skoffer *et al.*<sup>59</sup> in knee OA patients after 4 weeks of PRT and a mean change of 1.0 chairs stands was found by Bennell *et al.*<sup>60</sup> after 12 weeks of NEMEX also in knee OA patients, resulting in a difference between treatments of 1.5 chair stands. An SD of 2.52 for the 30 s CST is calculated from the 95% CI of the change in the intervention group of the study by Skoffer *et al.*<sup>59</sup> Given a power of 0.90 and two-sided significance level  $\alpha=0.05$ , the estimated sample size for a two-sample means test comparing PRT to NEMEX yields 122 participants. With an anticipated dropout rate of 30%, a total of 160 participants is the estimated sample size. For the primary 12-month comparison, the difference between groups receiving booster sessions and groups not receiving booster sessions is expected to be larger than for the comparison of PRT and NEMEX. Hence, we expect this study to be adequately powered for both comparisons.

### Statistical analysis

An intention-to-treat approach will be used for analysing all changes in primary and secondary outcome measures including all enrolled participants according to randomisation group. Between-group comparisons of change from baseline to follow-up in the primary and secondary continuous outcomes will be analysed using a repeated measures mixed model with participants, clusters and sites as random effects, visits and treatment arms (that is treatment in case of the 3-month follow-up and the interaction between treatment and EBS for the 12-month follow-up) as fixed effects. Descriptive statistics for baseline demographics and clinical characteristics will be used to assess comparability of the groups and to adjust for potential confounders in per-protocol analyses. A per-protocol analysis will be conducted on participants who have a high adherence to interventions ( $\geq 80\%$ ) and have not undergone hip surgery. Data will be tested for normal

distribution. The statistical level of significance will be set to  $p<0.05$  and outcomes will be presented as means with 95% CIs. A difference in mean change between groups in the 30 s CST of 2.1 chair stands is considered a major clinically important improvement (MCII), as defined by Wright *et al.*<sup>46</sup> To further guide the clinical interpretation, difference between groups in proportions of patients achieving the MCII for within-patients score change, as defined by Wright *et al.* of 2.6 chair stands,<sup>46</sup> will be analysed using a threshold of 20% between-group difference.<sup>61</sup> Less than 20% is regarded as no meaningful difference between treatments and  $\geq 20\%$  as a meaningful difference between treatments. Furthermore, we will calculate the trial-specific minimal important difference by subtracting the mean 30 s CST score for participants reporting to have experienced a 'small but not important change' in GPE from those reporting 'important change' in GPE at 3 months. The statistical analyses and interpretation of data will be blinded to group allocation.<sup>62</sup>

### Economic evaluation of interventions

The economic evaluation will be performed from both a societal perspective and a healthcare perspective and will use the intention-to-treat principle. An incremental cost-utility ratio will be calculated by dividing the difference in costs by the difference in effects. Cost of healthcare utilisation, productivity loss and total costs will be estimated. The EQ-5D-5L will be used to calculate quality-adjusted life-years (QALYs). Danish population norms will be used to calculate QALYs using linear interpolation between measurement points. Missing data will be imputed using multiple imputations by chained equations using Rubin's rules.<sup>63</sup> In order to account for the possible clustering of data, analyses will be performed using linear mixed models.<sup>64</sup> Accounting for the possible clustering of data (eg, at the hospital level) is very important, as most economic evaluations fail to do so, whereas ignoring the possible clustering of data might lead to inaccurate levels of uncertainty and inaccurate point estimates.<sup>64</sup> Bootstrapping techniques will be used to estimate the uncertainty surrounding the cost-effectiveness estimates; cost-effectiveness planes and cost-effectiveness acceptability curves will be presented. Various one-way sensitivity analyses will be performed to test the robustness of the study results (eg, complete-case analysis and per-protocol analysis). The 12-month intervention period is the time horizon of the analysis. The economic evaluation will be performed in STATA and R.

### Patient involvement

Before developing the design for this trial, two focus group interviews were conducted with patients with hip OA exercising at physiotherapy clinics. Open-ended questions were asked regarding optimal delivery of the exercise interventions, meaningful outcome measures and practical considerations, that is, how far they would commute for exercise and test sessions. These considerations guided the design of this trial.



## Ethical aspects and dissemination

The trial has been approved by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 1-10-72-267-20). Results will be published in international peer-reviewed scientific journals regardless of positive, negative or inconclusive results. Authorship eligibility will be based on the recommendations from the International Committee of Medical Journal Editors.

## DISCUSSION

This is the first trial to investigate the effectiveness of PRT compared with NEMEX and the effectiveness of EBS in patients with hip OA compared with a group with a matching initial intervention but without EBS. This study will contribute with novel and clinically important evidence enabling evidence-based recommendations and implementation of specific exercise modalities.

One of the major strengths of this trial is the multi-centre, randomised, controlled, assessor blinded, design with participants recruited from four hospitals and 10 clinics making the findings highly generalisable to patients treated in the healthcare system. Moreover, the long-term follow-up will provide insights into the sustainability of the effects of exercise as treatment in hip OA and whether EBS can address the common problem of exercise effects diminishing over time.<sup>20</sup> Lastly, the cost-effectiveness assessment will provide important information on societal costs associated with implementation of the interventions in healthcare systems and whether the effects are worth the costs.

The limitations of this trial are that the physiotherapists delivering the interventions and the participants receiving the interventions cannot be blinded to treatment allocation due to the nature of exercise interventions. This may introduce performance bias, especially in the patient-reported outcomes. However, the primary outcome and other functional performance tests are objective outcome measurements and less affected by performance bias. Second, there is no passive control group in this trial and as such, we can only compare the effects of the exercise modalities and not distinguish between the specific treatment effects and the contextual effects. Third, the sample size only provides power to detect a difference between PRT and NEMEX of 1.5 chair stands while the MCII has been found to be 2.1 chair stands.<sup>46</sup> Hence, the clinical relevance of a difference in mean change of 1.5 chair stands is uncertain. Consequently, the clinical interpretation will also include a comparison of the proportion of patients in each group reaching the threshold for MCII and a trial specific minimal important difference is calculated. Fourth, the comparison of PRT and NEMEX as EBS is not only a comparison of exercise type but also different modes of delivery since participants are either given a fitness membership (PRT) or equipment to exercise at home (NEMEX). Hence, the setup and surroundings are different and will affect the comparison.

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**Competing interests** TK, IM and UD have previously worked extensively with progressive resistance training and STS has done the same with neuromuscular exercise and is co-lead of the Danish initiative, Good Life with osteoArthritis in Danmark (GLA:D), which entails neuromuscular exercise.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Consent obtained directly from patient(s)

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## REFERENCES

- <sup>1</sup> Katz JN, Arant KR, Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: a review. *JAMA* 2021;325:568–78.
- <sup>2</sup> Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet* 2019;393:1745–59.
- <sup>3</sup> Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage* 2019;27:1578–89.

- 4 Fernandes L, Hagen KB, Bijlsma JWJ, *et al.* EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Ann Rheum Dis* 2013;72:1125–35.
- 5 Kolasinski SL, Neogi T, Hochberg MC, *et al.* 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol* 2020;72:220–33.
- 6 Fransen M. Exercise for osteoarthritis of the hip. *Cochrane Database Syst Rev* 2014;4:CD007912.
- 7 Moseng T, Dagfinrud H, Smedslund G, *et al.* The importance of dose in land-based supervised exercise for people with hip osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis Cartilage* 2017;25:1563–76.
- 8 Bieler T, Siersma V, Magnusson SP, *et al.* In hip osteoarthritis, Nordic walking is superior to strength training and home-based exercise for improving function. *Scand J Med Sci Sports* 2017;27:873–86.
- 9 Fukumoto Y, Tateuchi H, Ikezoe T, *et al.* Effects of high-velocity resistance training on muscle function, muscle properties, and physical performance in individuals with hip osteoarthritis: a randomized controlled trial. *Clin Rehabil* 2014;28:48–58.
- 10 Skou ST, Roos EM. Good Life with osteoArthritis in Denmark (GLA:D™): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC Musculoskelet Disord* 2017;18:72.
- 11 Villadsen A, Overgaard S, Holsgaard-Larsen A, *et al.* Immediate efficacy of neuromuscular exercise in patients with severe osteoarthritis of the hip or knee: a secondary analysis from a randomized controlled trial. *J Rheumatol* 2014;41:1385–94.
- 12 Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patients with severe hip or knee oa: the individualized goal-based NEMEX-TJR training program. *BMC Musculoskelet Disord* 2010;11:126.
- 13 Ageberg E, Nilsdotter A, Kosek E, *et al.* Effects of neuromuscular training (NEMEX-TJR) on patient-reported outcomes and physical function in severe primary hip or knee osteoarthritis: a controlled before-and-after study. *BMC Musculoskelet Disord* 2013;14:232.
- 14 Hermann A, Holsgaard-Larsen A, Zerahn B, *et al.* Preoperative progressive explosive-type resistance training is feasible and effective in patients with hip osteoarthritis scheduled for total hip arthroplasty—a randomized controlled trial. *Osteoarthritis Cartilage* 2016;24:91–8.
- 15 Foley A, Halbert J, Hewitt T, *et al.* Does hydrotherapy improve strength and physical function in patients with osteoarthritis—a randomised controlled trial comparing a gym based and a hydrotherapy based strengthening programme. *Ann Rheum Dis* 2003;62:1162–7.
- 16 Hansen S, Mikkelsen LR, Overgaard S, *et al.* Effectiveness of supervised resistance training for patients with hip osteoarthritis - a systematic review. *Dan Med J* 2020;67. [Epub ahead of print: 01 Jun 2020].
- 17 Loureiro A, Mills PM, Barrett RS. Muscle weakness in hip osteoarthritis: a systematic review. *Arthritis Care Res* 2013;65:340–52.
- 18 McKendry J, Stokes T, Mcleod JC, *et al.* Resistance exercise, aging, disuse, and muscle protein metabolism. *Compr Physiol* 2021;11:2249–78.
- 19 Svege I, Fernandes L, Nordsletten L, *et al.* Long-Term effect of exercise therapy and patient education on impairments and activity limitations in people with hip osteoarthritis: secondary outcome analysis of a randomized clinical trial. *Phys Ther* 2016;96:818–27.
- 20 Goh S-L, Persson MSM, Stocks J, *et al.* Efficacy and potential determinants of exercise therapy in knee and hip osteoarthritis: a systematic review and meta-analysis. *Ann Phys Rehabil Med* 2019;62:356–65.
- 21 Pisters MF, Veenhof C, Schellevis FG, *et al.* Exercise adherence improving long-term patient outcome in patients with osteoarthritis of the hip and/or knee. *Arthritis Care Res* 2010;62:1087–94.
- 22 Laurits Taul-Madsen TK, Skou ST, Mechlenburg I. Exercise booster sessions as a mean to maintain the effect of an exercise-intervention - A systematic review. *Physical Therapy Reviews* 2021.
- 23 Abbott JH, Chapple CM, Fitzgerald GK, *et al.* The incremental effects of manual therapy or booster sessions in addition to exercise therapy for knee osteoarthritis: a randomized clinical trial. *J Orthop Sports Phys Ther* 2015;45:975–83.
- 24 Bove AM, Smith KJ, Bise CG, *et al.* Exercise, manual therapy, and booster sessions in knee osteoarthritis: cost-effectiveness analysis from a multicenter randomized controlled trial. *Phys Ther* 2018;98:16–27.
- 25 Pisters MF, Veenhof C, Schellevis FG, *et al.* Long-Term effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a randomized controlled trial comparing two different physical therapy interventions. *Osteoarthritis Cartilage* 2010;18:1019–26.
- 26 Abbott JH, Robertson MC, Chapple C, *et al.* Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: a randomized controlled trial. 1: clinical effectiveness. *Osteoarthritis Cartilage* 2013;21:525–34.
- 27 Juhakoski R, Tenhonen S, Malmivaara A, *et al.* A pragmatic randomized controlled study of the effectiveness and cost consequences of exercise therapy in hip osteoarthritis. *Clin Rehabil* 2011;25:370–83.
- 28 Teirlinck CH, Luijsterburg PAJ, Dekker J, *et al.* Effectiveness of exercise therapy added to general practitioner care in patients with hip osteoarthritis: a pragmatic randomized controlled trial. *Osteoarthritis Cartilage* 2016;24:82–90.
- 29 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- 30 Slade SC, Dionne CE, Underwood M, *et al.* Consensus on exercise reporting template (CERT): explanation and elaboration statement. *Br J Sports Med* 2016;50:1428–37.
- 31 Toigo M, Boutellier U. New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. *Eur J Appl Physiol* 2006;97:643–63.
- 32 Schulz KF, Altman DG, Moher D, *et al.* CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;8:18.
- 33 National Institute for health and clinical excellence, in osteoarthritis: care and management in adults. 2014: London.
- 34 Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. *Scand J Work Environ Health* 1990;16 Suppl 1:55–8.
- 35 Ageberg E, Roos EM. Neuromuscular exercise as treatment of degenerative knee disease. *Exerc Sport Sci Rev* 2015;43:14–22.
- 36 Garber CE, Blissmer B, Deschenes MR, *et al.* American College of sports medicine position stand. quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43:1334–59.
- 37 American College of Sports, M, American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009;41:687–708.
- 38 Dobson F, Hinman RS, Roos EM, *et al.* OARSI recommended Performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1042–52.
- 39 Gill S, McBurney H. Reliability of Performance-based measures in people awaiting joint replacement surgery of the hip or knee. *Physiother Res Int* 2008;13:141–52.
- 40 Jones CJ, Rikli RE, Beam WC. A 30-S chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999;70:113–9.
- 41 Burgess LC, Taylor P, Wainwright TW, *et al.* Strength and endurance deficits in adults with moderate-to-severe hip osteoarthritis, compared to healthy, older adults. *Disabil Rehabil* 2021:1–8.
- 42 Judd DL, Thomas AC, Dayton MR, *et al.* Strength and functional deficits in individuals with hip osteoarthritis compared to healthy, older adults. *Disabil Rehabil* 2014;36:307–12.
- 43 Clynes MA, Jameson KA, Edwards MH, *et al.* Impact of osteoarthritis on activities of daily living: does joint site matter? *Aging Clin Exp Res* 2019;31:1049–56.
- 44 Nilsdotter AK, Lohmander LS, Klässbo M, *et al.* Hip disability and osteoarthritis outcome score (HOOS)—validity and responsiveness in total hip replacement. *BMC Musculoskelet Disord* 2003;4:10.
- 45 Thorborg K, Roos EM, Bartels EM, *et al.* Validity, reliability and responsiveness of patient-reported outcome questionnaires when assessing hip and groin disability: a systematic review. *Br J Sports Med* 2010;44:1186–96.
- 46 Wright AA, Cook CE, Baxter GD, *et al.* A comparison of 3 methodological approaches to defining major clinically important improvement of 4 performance measures in patients with hip osteoarthritis. *J Orthop Sports Phys Ther* 2011;41:319–27.
- 47 Bieler T, Magnusson SP, Kjaer M, *et al.* Intra-rater reliability and agreement of muscle strength, power and functional performance measures in patients with hip osteoarthritis. *J Rehabil Med* 2014;46:997–1005.
- 48 Bassey EJ, Short AH. A new method for measuring power output in a single leg extension: feasibility, reliability and validity. *Eur J Appl Physiol Occup Physiol* 1990;60:385–90.
- 49 Foldvari M, Clark M, Laviolette LC, *et al.* Association of muscle power with functional status in community-dwelling elderly women. *J Gerontol A Biol Sci Med Sci* 2000;55:M192–9.

- 50 Barbalho M, Gentil P, Raiol R, *et al.* High 1RM tests reproducibility and validity are not dependent on training experience, muscle group tested or strength level in older women. *Sports* 2018;6:171.
- 51 Kamper SJ, Ostelo RWJG, Knol DL, *et al.* Global perceived effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol* 2010;63:760–6.
- 52 The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Integrated addendum to ICH E6(R1): Guideline for good clinical practice 2016.
- 53 Olsson SJG, Ekblom Örjan, Andersson E, *et al.* Categorical answer modes provide superior validity to open answers when asking for level of physical activity: a cross-sectional study. *Scand J Public Health* 2016;44:70–6.
- 54 Hawker GA, Mian S, Kendzerska T, *et al.* 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:S240–52.
- 55 Goossens ME, Rutten-van Mölken MP, Vlaeyen JW, *et al.* The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. *J Clin Epidemiol* 2000;53:688–95.
- 56 Bouwmans C, Krol M, Severens H, *et al.* The iMTA productivity cost questionnaire: a standardized instrument for measuring and Valuing health-related productivity losses. *Value Health* 2015;18:753–8.
- 57 Conner-Spady BL, Marshall DA, Bohm E, *et al.* Reliability and validity of the EQ-5D-5L compared to the EQ-5D-3L in patients with osteoarthritis referred for hip and knee replacement. *Qual Life Res* 2015;24:1775–84.
- 58 Herdman M, Gudex C, Lloyd A, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
- 59 Skoffer B, Maribo T, Mechlenburg I, *et al.* Efficacy of preoperative progressive resistance training on postoperative outcomes in patients undergoing total knee arthroplasty. *Arthritis Care Res* 2016;68:1239–51.
- 60 Bennell KL, Kyriakides M, Metcalf B, *et al.* Neuromuscular versus quadriceps strengthening exercise in patients with medial knee osteoarthritis and varus malalignment: a randomized controlled trial. *Arthritis Rheumatol* 2014;66:950–9.
- 61 Felson DT, Anderson JJ, Boers M, *et al.* American College of rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.
- 62 Järvinen TLN, Sihvonen R, Bhandari M, *et al.* Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. *J Clin Epidemiol* 2014;67:769–72.
- 63 White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;30:377–99.
- 64 Gomes M, Grieve R, Nixon R, *et al.* Methods for covariate adjustment in cost-effectiveness analysis that use cluster randomised trials. *Health Econ* 2012;21:1101–18.