Progressive resistance training compared to neuromuscular exercise in patients with hip osteoarthritis, and the additive effect of exercise booster sessions (The Hip Booster Trial)

Statistical analysis plan

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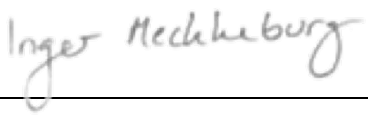
Chief investigator / Clinical lead	Inger Mechlenburg	12-10-2022	

Background and rationale

Exercise is an effective treatment for participants with hip osteoarthritis (OA), reducing pain and improving physical function [1]. Content and dosage of exercise interventions seem to be important for the magnitude of the effects [2]. However, very few exercise modalities have been compared [3, 4] and recommendations suggesting one type of exercise over another are not based on solid evidence [5].

Neuromuscular exercise (NEMEX) and progressive resistance training (PRT) have been shown to improve physical function and alleviate symptoms in participants with hip OA [6-11]. The observed muscle atrophy and weakness in participants with hip OA [12] offer a rationale for PRT being superior to NEMEX, since PRT is generally considered the most potent intervention to increase muscle mass and strength [13]. However, no prior randomized, controlled trial (RCT) has assessed whether PRT is superior to NEMEX in improving functional performance in participants with hip OA.

A substantial challenge related to the application of exercise interventions in hip OA is that effects are typically not maintained long-term [14, 15]. One proposed solution is exercise booster sessions (EBS), which is training sessions provided regularly throughout the follow-up period aiming to sustain effects of the preceding exercise intervention [16]. In knee OA, there is some evidence to suggest that EBS may decrease pain and self-reported disability [17] and lead to cost savings for the healthcare system [18]. EBS may be an effective intervention to improve long-term effects of exercise in hip OA, but this remains to be elucidated.

Objectives

The primary objective of this RCT is to investigate the effectiveness of 3 months of PRT compared to NEMEX on functional performance in participants with hip OA. A secondary objective is to investigate the effectiveness of EBS in prolonging the effects of the initial exercise interventions.

The primary hypothesis for the 3-month comparison is that PRT is superior to NEMEX in improving functional performance, measured by the 30-second chair stand test.

The primary hypothesis for the 12-month comparison is that EBS are superior to no EBS in improving functional performance, measured by the 30s-CST, regardless of allocation to PRT or NEMEX.

Secondary hypotheses for the 12-month comparisons are:

1. PRT is superior to NEMEX in improving functional performance, measured by the 30s-CST, regardless of allocation to EBS or no EBS.

2. PRT followed by EBS is superior to PRT without EBS, and NEMEX followed by EBS is superior to NEMEX without EBS in improving functional performance, measured by the 30s-CST.

STUDY METHODS

Trial design

This multicenter, cluster-randomized, controlled, parallel group, assessor-blinded, superiority trial will be conducted at five hospitals and ten physiotherapy clinics across Denmark. Participants will be cluster-randomized to a 3-month intervention of either PRT or NEMEX and additionally to receive EBS or not, resulting in four treatment arms (PRT, NEMEX, PRT+B and NEMEX+B). The primary outcome is change in functional performance, measured by the 30s-CST, and the primary endpoint is at three months after starting the intervention (i.e. immediately after 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-and 12-month follow-up. The exercise interventions are described in detail in the trial protocol.

Randomization

After recruitment and baseline assessment, participants will be randomized to either PRT, NEMEX, PRT+B or NEMEX+B by cluster-randomization 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 enroll participants. The cluster size is set at five participants. However, to keep the waiting time at an acceptable level, groups of one to four participants are cluster-randomized if they have waited >14 days after inclusion.

Sample size

The sample size calculation is based on the expected between-group difference in the 30s-CST change 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. [19] in knee OA patients after 4 weeks of PRT and a mean change of 1.0 chairs stands was found

by Bennell et al. [20] after 12 weeks of NEMEX also in knee OA patients, resulting in a difference between treatments of 1.5 chair stands. A standard deviation of 2.52 for the 30s-CST is calculated from the 95% CI of the change in the intervention group of the study by Skoffer et al. [19]. Given a power of 0.90 and two-sided significance level α=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 this comparison as well.

Statistical interim analysis and stopping guidance

No formal statistical interim analysis is planned. Participant enrolment started January 2021 and is expected to be completed by May 2022. All participants are expected to have completed 12-month follow-up assessments by August 2023.

Timing of final analysis

For the 3-month comparison, the final analysis is planned to be conducted when all randomized participants have completed 3-month follow-up. The anticipated publication submission time is ultimo 2022. For the 12-month comparison, the final analysis is planned when all randomized participants have completed 12-month follow-up. The anticipated publication submission time is ultimo 2023.

Timing of outcome assessments

This trial entails outcome assessments at baseline and at 3- and 12-months after the first exercise session. A description of outcome assessments and the timing is presented in table 2 in the trial protocol.

STATISTICAL PRINCIPLES

Confidence intervals

All statistical tests and confidence intervals will be two-sided. The statistical level of significance will be set to *0.05* and outcomes will be presented as means with 95% confidence intervals.

Adherence and protocol deviations

Adherence to training will be registered by the physiotherapists supervising the exercise sessions and presented as descriptive statistics (numbers and percentages). Adherence % is calculated by: Number of sessions completed / number of sessions planned x 100%. High adherence for the initial three 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-administered exercise sessions. Moderate adherence is defined as participation in 50 to <80% of the sessions and poor adherence as <50% of the sessions. High adherence for the booster sessions is defined as participation in ≥ three of these sessions, while moderate adherence is defined as two sessions, and poor adherence as less than two sessions. In addition, exercise fidelity is defined as number of sets completed out of the total number of prescribed sets and will be registered and presented (numbers and percentages), using the same calculation and cut-offs as for adherence during the initial three months. Specifically, for NEMEX, proportion of patients reaching difficulty level 1, 2, 3 and 4 will be presented, while numbers of prescribed repetitions completed and exercise intensity will be presented for PRT. Further, any protocol deviations; drop-outs, surgery or initiation of other treatments, will also be presented as descriptive statistics (numbers and percentages).

Analysis populations

The primary analyses will follow the Intention to Treat (ITT) principle, including all participants randomized to treatment in the analyses, regardless of adherence to treatment or any protocol deviations. Participants who drop out, will contribute with data to their respective groups until they drop out and imputations will not be applied. Additionally, per protocol analyses will be performed including only participants with high adherence to the exercise sessions (≥80% of the planned sessions completed), high exercise fidelity (≥ 80% of prescribed repetitions performed) and excluding participants undergoing surgery.

TRIAL POPULATION

Screening data

All participants screened for eligibility at the four hospitals and ten clinics will be presented in a CONSORT flowchart (see Recruitment).

Eligibility

Participants meeting the following inclusion and exclusion criteria are considered eligible for this trial:

Inclusion criteria: (1) Clinically diagnosed OA of the hip joint according to the National Institute for Health and Care Excellence criteria [21]; (2) An event of pain during activity of at least 3 out of 10 on a Numerical Rating Scale (NRS) in the index hip within the last two weeks; (3) Age ≥ 45 years; (4) No hip joint morning stiffness or less than 30 minutes; (5) No surgery in the lower extremities six months prior to inclusion; (6) No comorbidity that markedly affects hip function; (7) Adequacy in written and spoken Danish; (8) Not being a candidate for total hip arthroplasty.

Exclusion criteria: (1) BMI score > 40; (2) Pregnancy; (3) PRT or NEMEX for the lower extremities exceeding 12 sessions over the last six months or six sessions over the last three months; (4) Planned vacation for more than 14 days within the initial 3-month intervention period without the possibility of prolonging the intervention accordingly.

Recruitment

The following information will be presented in the CONSORT flowchart in total number of participants who were: (1) screened, (2) excluded (with reasons), (3) randomized, (4) received allocated treatment, (5) discontinued intervention (with reasons), (6) lost to follow-up (with reasons), (7) included in ITT analysis and (8) included in per protocol analysis.

Withdrawal/follow-up

Participants deciding to withdraw from the trial will be asked to complete outcome assessments even though they stop attending exercise sessions. As such, participants who withdraw will be of

two categories: (1) participants withdrawing from an exercise intervention but still attending outcome assessments and (2) participants withdrawing entirely from the trial and not attending outcome assessments. Timing and reasons for withdrawals and participants lost to follow-up will be presented in the CONSORT flowchart for the primary follow-up points at 3 and at 12 months.

Baseline participant characteristics

Baseline participant characteristics will be presented by randomization group entailing the following information: Gender, age, height, weight, civil status, educational level, employment status, substance use, duration of symptoms, unilateral/bilateral hip OA, previous treatment, pain medication, joint replacements, and other diseases. For categorical variables, numbers and percentages will be presented. For continuous variables, means and standard deviations will be presented if data follows a normal distribution. If continuous variables are not normally distributed, medians and interquartile ranges are presented. Baseline results for the primary and secondary outcomes will be presented as part of the analysis.

ANALYSIS

Outcome definitions

Primary outcome

30-second chair stand test (30s-CST)

The primary outcome is between-group difference in change from baseline to 3 and 12 months in the 30s-CST (number of repetitions). The 30s-CST is a valid and responsive measure with excellent reliability evaluating sit-to-stand function [22-24]. A difference in mean change between groups in the 30s-CST of 2.1 chair stands is considered a major clinically important improvement, as defined by Wright et al [25]. To further guide the clinical interpretation, differences between groups in proportions of participants achieving the major clinically important improvement for within-participants score change, as defined by Wright et al. of 2.6 chair stands [25], will be analyzed using a threshold of 20% between-group difference [26]. Less than 20% is regarded as no meaningful difference between treatments and ≥ 20% as a meaningful difference between treatments. Furthermore, we will calculate the trial-specific minimal important difference by subtracting the mean 30s-CST score for participants reporting to have experienced a ‘small but not important

change' in global perceived effect (GPE) from those reporting 'important change' in GPE at 3 months.

Key secondary outcomes

Hip disability and Osteoarthritis Outcomes Score (HOOS)

A secondary outcome is the between-group difference in change from baseline to 3 and 12 months in the subscales of the HOOS questionnaire. HOOS is a 40-item patient-reported questionnaire consisting of five subscales: Symptoms, pain, activities of daily life function, sport/recreation and hip-related quality of life. Each subscale gives a score ranging from 0 (worst) to 100 (best) [49]. HOOS is a valid, reliable and responsive measure in participants with hip OA [30]. The pain and hip-related quality of life subscales are chosen as key secondary outcomes and will be mentioned in the conclusion, but secondary to the primary outcome.

Secondary outcomes

Hip disability and Osteoarthritis Outcomes Score (HOOS)

A secondary outcome is the between-group difference in change from baseline to 3 and 12 months in the symptoms, activities of daily life function and sport/recreation subscales.

40-meter fast-paced walk test (40m-FPWT)

A secondary outcome is the between-group difference in change from baseline to 3 and 12 months in the 40m-FPWT (in seconds). The 40m-FPWT measures the total time it takes to walk 4×10 meters, excluding turns. It is a valid and responsive measure of short distance maximum walking speed with excellent reliability [25].

9-step timed stair climb test (9-step TSCT)

A secondary outcome is the between-group difference in change from baseline to 3 and 12 months in the 9-step TSCT (in seconds). The 9-step TSCT measures the time spent to ascend and descend nine steps and has excellent reliability in participants with symptomatic hip OA [27].

Nottingham Leg Extensor Power Rig (NLEPR)

A secondary outcome is the between-group difference in change from baseline to 3 and 12 months in leg extensor muscle power (watt/kg body weight), measured by the NLEPR. The NLEPR test has excellent reliability in participants with symptomatic hip OA [45, 46]. Leg extensor muscle power is a clinically important measure strongly correlated to physical function [28].

Unilateral one-repetition-maximum leg press

A secondary outcome is the between-group difference in change from baseline to 3 and 12 months in maximal leg extensor strength of the index hip (kg weight lifted), measured by a one-repetition-maximum test in a leg press resistance training machine, which is a highly reliable test in elderly populations [29].

Global perceived effect (GPE)

A secondary outcome is the proportion of participants in each group experiencing a "meaningful improvement" at 3 and 12 months in GPE. GPE will be assessed for three domains; pain, activities of daily living and quality of life, on a 7-point Likert scale [31].

Adverse events (AE) and serious adverse events (SAE)

Throughout the trial there will be continuous registration of AE and SAE as defined by The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [32]. Physiotherapists supervising the exercise sessions will monitor events. During the 3- and 12-months 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 [33].

Adherence and drop-outs

Adherence to training will be monitored by the physiotherapists supervising the exercise sessions. This is described in detail in *Adherence and protocol deviations*.

Analysis methods

An intention-to-treat approach will be used for analyzing all changes in primary and secondary outcome measures including all enrolled participants according to randomization group. Between-group comparisons of change from baseline to follow-up in the primary and secondary continuous outcomes will be analyzed using a repeated measures mixed effect model with participants, clusters and sites as random effects and with visits and treatment arms as fixed effects. A per-protocol analysis will be conducted on participants who complete the intervention with a high adherence (≥ 80%) to exercise sessions, high exercise fidelity (≥ 80% of prescribed sets performed) and who have not undergone hip surgery.

Descriptive statistics for baseline demographics and clinical characteristics will be used to assess comparability of the groups and to adjust for potential confounders in secondary per-protocol analyses. Normal distribution of the residuals will be assessed by visual inspection of quantile plots and histograms. The statistical analyses and interpretation of data for the primary 3- and 12-month analyses will be blinded to group allocation [34]. However, the comparison of NEMEX and PRT at 12 months will not be performed as a blinded analysis, because the authors will be able to identify which group is which, from the baseline values found prior when analyzing the 3-month changes.

Missing data

No imputations will be applied in the analysis. Each randomized participant will be included in the intention-to-treat analysis with the data collected for the participant. An attempt to collect data from all randomized participants will be made, regardless of adherence to interventions.

Additional analysis

No additional analyses are planned for the 3- and 12-month follow-up.

Statistical software

All statistical analyses will be performed in Stata (Statacorp, College Station, Texas, USA).

Figures and tables for 3-month comparison

Figure 1. Flowchart of all participants screened for the trial.

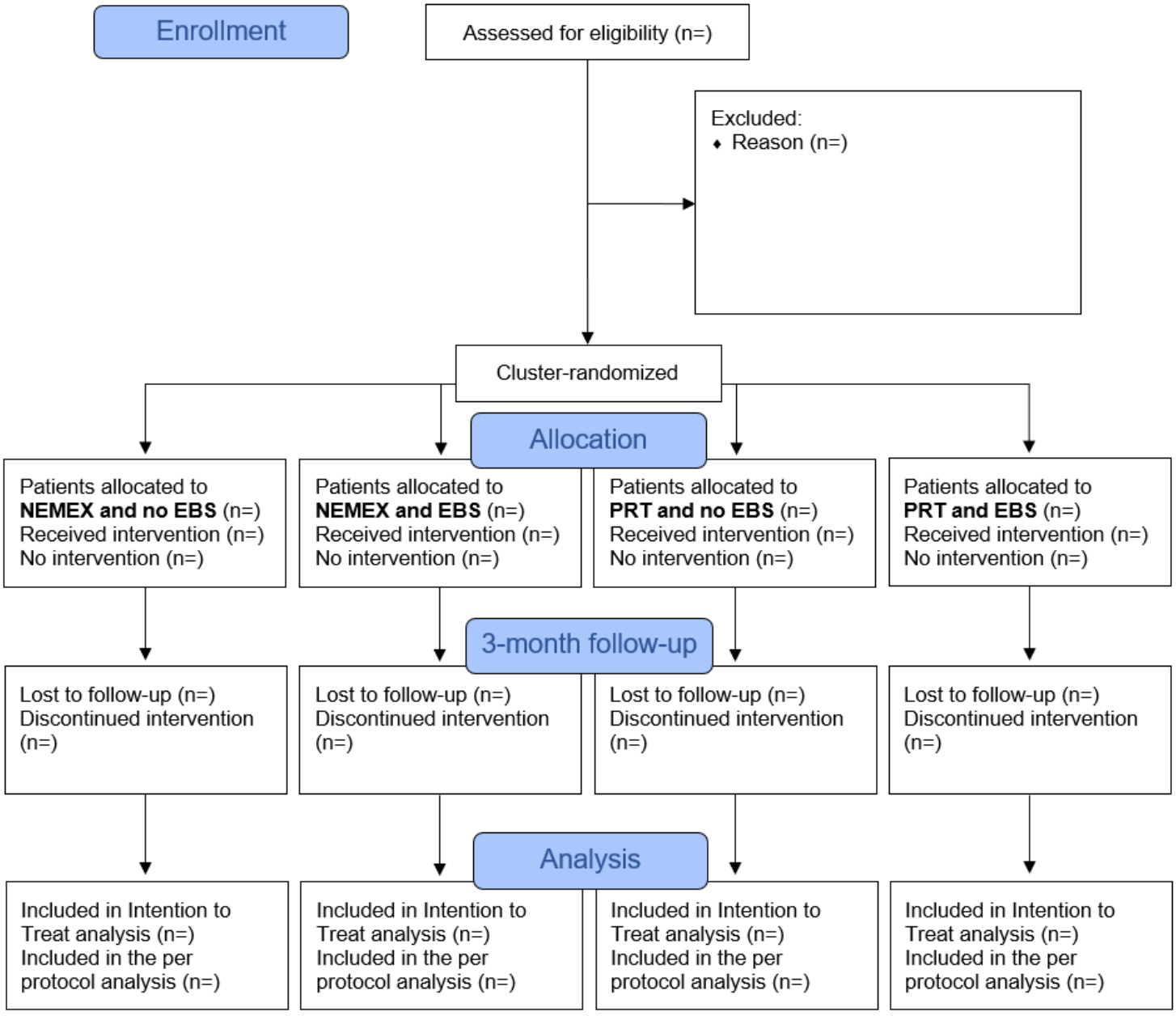


Figure 2. Change in 30 second chair stand test from baseline to 3-month follow-up. This figure is an example and shows the anticipated changes.

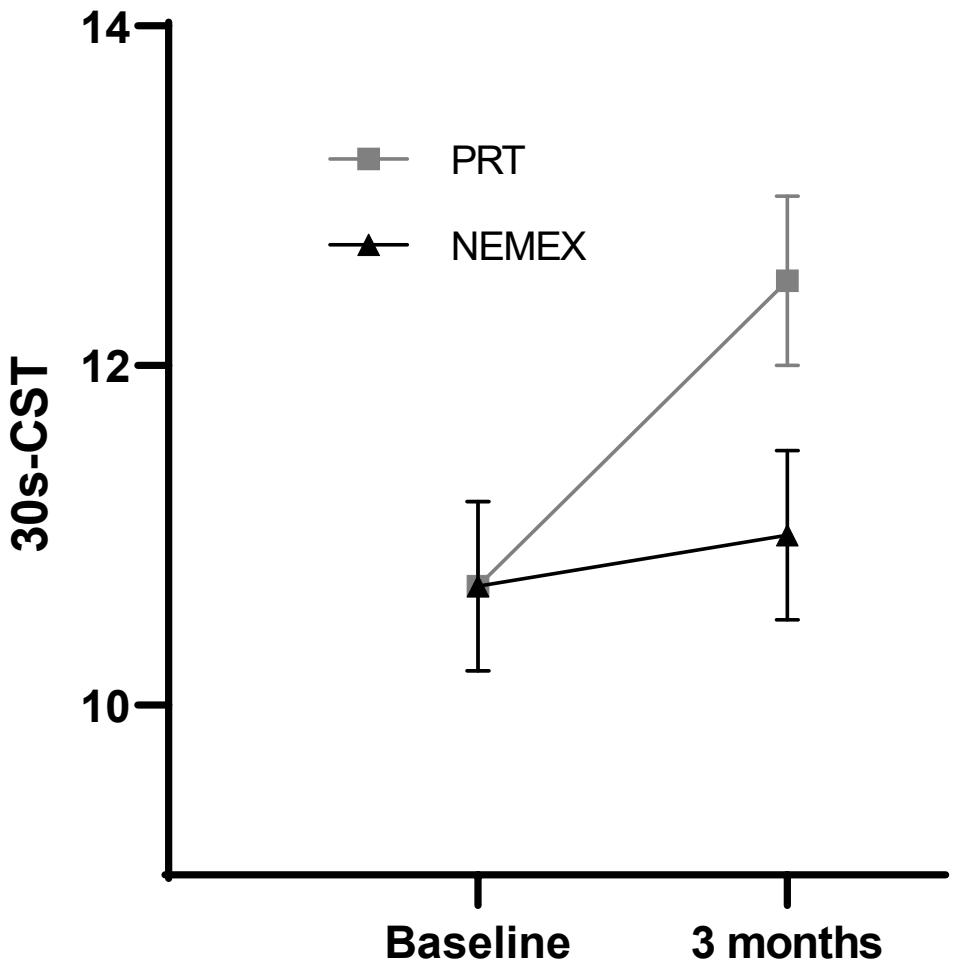


Figure 3. Proportion of participants reaching the clinically relevant improvement in primary and secondary outcomes. This figure is an example and shows the anticipated changes.

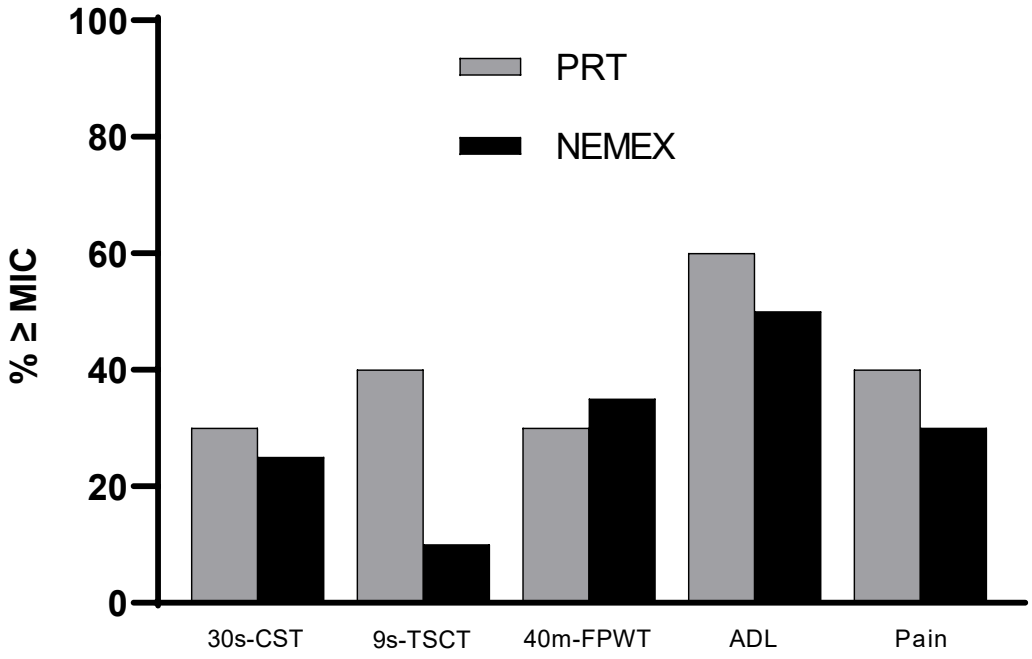


Table 1. Baseline Characteristics.

	Neuromuscular exercise (n=)	Progressive resistance training (n=)
Women – n (%)		
Age – years		
Height – meters		
Weight – kilograms		
Hip osteoarthritis		
Unilateral		
Bilateral		
Duration of symptoms		
0-12 months		
1-2 years		
2-5 years		
More than 5 years		
Civil status		
Married or cohabiting		
Single		
Not reported		
Educational level		
Primary school		
Vocational education		
High school or similar		
Higher education		
Employment status		
Student/under education		
Working		
Not working		
Retired		
Smoking behavior		
Smoking		
Not smoking		
Previous treatment		
Exercise		
Physiotherapy		
Corticoidsteroid injection		
Surgery		
Contralateral THA		
Arthroscopy		
Current pain medication		
Paracetamol		
NSAID		
Opioids		
Other		
Comorbidities		
Specification - n (%)		
Specification – n (%)		
Physical activity (weekly)		
≥150 min moderate-intensity - n (%)		
≥60 min vigorous-intensity – n (%)		
≥90 min vigorous-intensity – n (%)		
Sedentary behavior (daily)		
≥10 hours - n (%)		
≥7 hours n (%)		

Table 2. Change from Baseline to 3-month follow-up in primary and secondary outcomes.

	Neuromuscular exercise			Progressive resistance training			Difference in change
Intention to treat analysis							
	Baseline (SD)	3-mo (SD)	Change (CI)	Baseline (SD)	3-mo (SD)	Change (CI)	Difference (CI)
Functional performance							
30 s chair stand test (PO)							
40 m fast-paced walk test							
9-step timed stair climb							
Nottingham Power Rig							
Unilateral 1RM leg press							
Patient-reported outcomes							
HOOS Symptoms							
HOOS Pain							
HOOS ADL function							
HOOS Sport/recreation							
HOOS Hip-related QoL							
Per-protocol analysis							
	Baseline (SD)	3-mo (SD)	Change (CI)	Baseline (SD)	3-mo (SD)	Change (CI)	Difference (CI)
Functional performance							
30 s chair stand test (PO)							
40 m fast-paced walk test							
9-step timed stair climb							
Nottingham Power Rig							
Unilateral 1RM leg press							
Patient-reported outcomes							
HOOS Symptoms							
HOOS Pain							
HOOS ADL function							
HOOS Sport/recreation							
HOOS Hip-related QoL							

Table 3. Adverse events, drop-outs and adherence to interventions.

	Neuromuscular exercise	Progressive resistance training
Serious adverse events – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Adverse events – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Drop-outs – n (%)		
Adherence to group sessions – n (%)		
≥ 80 % adherence – n (%)		
≥ 50 % adherence – n (%)		
< 50 % adherence – n (%)		
Proportion of sets completed – n (%)		
≥ 80 % – n (%)		
≥ 50 % – n (%)		
< 50 % – n (%)		
Number of joint replacements – n (%)		

Figures and tables for 12-month comparison

Figure 1. Flowchart of all participants screened for the trial.

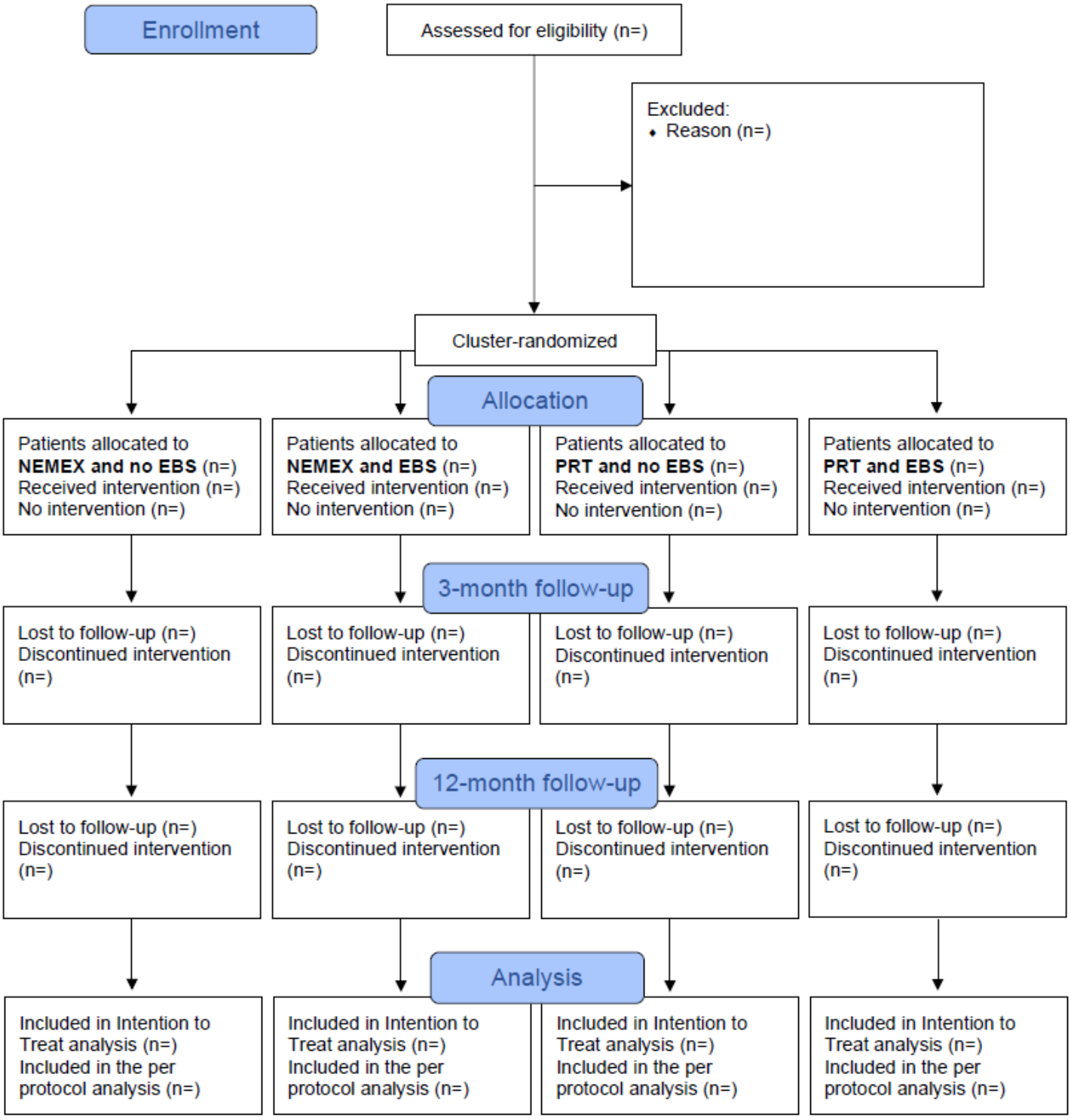


Figure 2. Change in 30 second chair stand test from baseline to 3- and 12-month follow-up. This figure is an example and shows the anticipated changes.

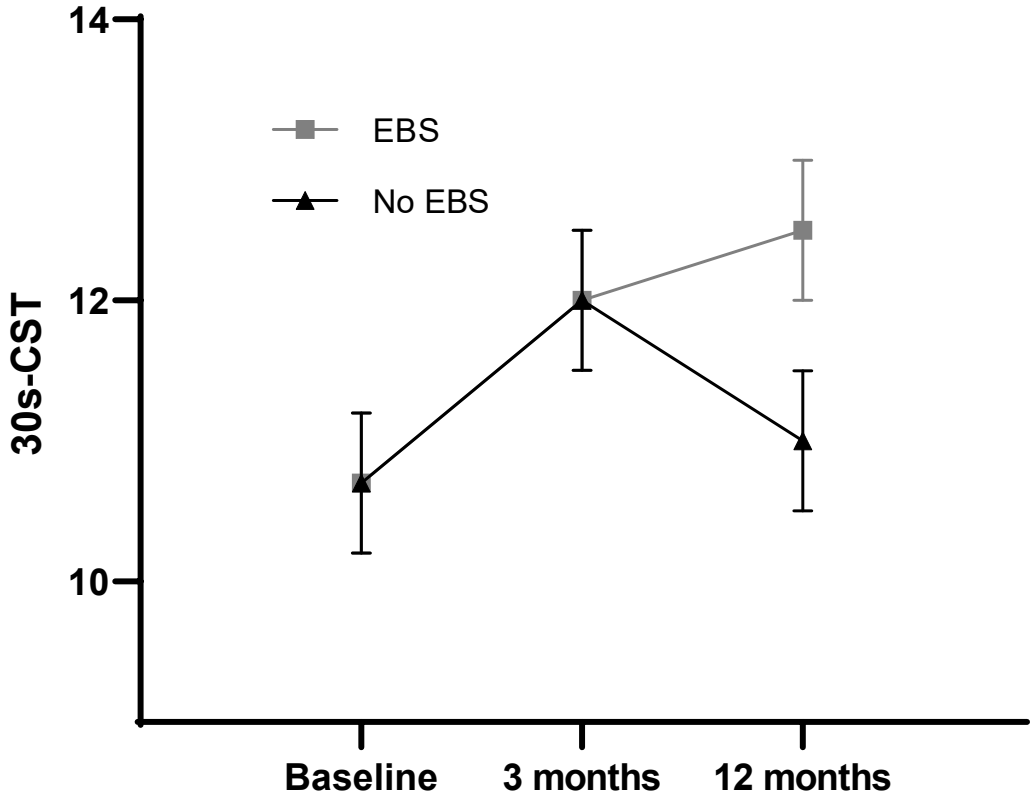


Table 1. Baseline Characteristics.

	Exercise booster sessions (n=)	No exercise booster sessions (n=)
Women – n (%)		
Age – years		
Height – meters		
Weight – kilograms		
Hip osteoarthritis		
Unilateral		
Bilateral		
Duration of symptoms		
0-12 months		
1-2 years		
2-5 years		
More than 5 years		
Civil status		
Married or cohabiting		
Single		
Not reported		
Educational level		
Primary school		
Vocational education		
High school or similar		
Higher education		
Employment status		
Student/under education		
Working		
Not working		
Retired		
Smoking behavior		
Smoking		
Not smoking		
Previous treatment		
Exercise		
Physiotherapy		
Corticoidsteroid injection		
Surgery		
Contralateral THA		
Arthroscopy		
Current pain medication		
Paracetamol		
NSAID		
Opioids		
Other		
Comorbidities		
Specification - n (%)		
Specification – n (%)		
Physical activity (weekly)		
≥150 min moderate-intensity - n (%)		
≥60 min vigorous-intensity – n (%)		
≥90 min vigorous-intensity – n (%)		
Sedentary behavior (daily)		
≥10 hours - n (%)		
≥7 hours n (%)		

Table 2. Change from Baseline to 12-month follow-up in primary and secondary outcomes

	Exercise booster sessions			No exercise booster sessions			Difference in change
Intention to treat analysis							
	3-mo (SD)	12-mo (SD)	Change (CI)	3-mo (SD)	12-mo (SD)	Change (CI)	Difference (CI)
Functional performance							
30 s chair stand test (PO)							
40 m fast-paced walk test							
9-step timed stair climb							
Nottingham Power Rig							
Unilateral 1RM leg press							
Patient-reported outcomes							
HOOS Symptoms							
HOOS Pain							
HOOS ADL function							
HOOS Sport/recreation							
HOOS Hip-related QoL							
Per-protocol analysis							
	3-mo (SD)	12-mo (SD)	Change (CI)	3-mo (SD)	12-mo (SD)	Change (CI)	Difference (CI)
Functional performance							
30 s chair stand test (PO)							
40 m fast-paced walk test							
9-step timed stair climb							
Nottingham Power Rig							
Unilateral 1RM leg press							
Patient-reported outcomes							
HOOS Symptoms							
HOOS Pain							
HOOS ADL function							
HOOS Sport/recreation							
HOOS Hip-related QoL							

Table 3. Adverse events, drop-outs and adherence to interventions.

	Exercise booster sessions	No exercise booster sessions
Serious adverse events – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Adverse events – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Specification – n (%)		
Drop-outs – n (%)		
Adherence to booster sessions – n (%)		
≥ 3 sessions– n (%)		
≥ 2 sessions – n (%)		
< 2 sessions – n (%)		
Adherence to self-administered sessions – n (%)		
≥ 80 % adherence – n (%)		
≥ 50 % adherence – n (%)		
< 50 % adherence – n (%)		
Proportion of sets completed – n (%)		
≥ 80 % – n (%)		
≥ 50 % – n (%)		
< 50 % – n (%)		
Number of joint replacements – n (%)		

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