Section 1: Administrative Information

Statistical analysis plan (SAP)

Effect of an exercise intervention targeting hip strengthening in patients undergoing revision total hip replacement – A multicenter randomized controlled trial (The Strong Hip Trial)

Martin Bækgaard Stisen[1,2], Inger Mechlenburg[1,2,3], and Erik Parner[4]

Affiliations

[1]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.

[2]Department of Orthopaedic Surgery, Aarhus University Hospital, Aarhus N, Denmark.

[3]Department of Public Health, Section of Sports, Aarhus University, Aarhus, Denmark.

[4]Department of Public Health, Section for Biostatistics, Aarhus University, Aarhus, Denmark.

Trial registration number

The trial is registered at www.clincaltrials.gov with the number NCT05657054.

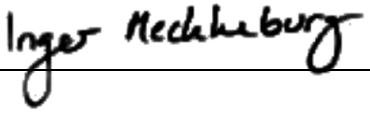
Version of protocol article used

This SAP was written based on the information in the trial protocol version 1.2, dated 19th of April 2024.

SAP revision history

No revisions have been made.

Roles, responsibilities, and signatures

Role	Name	Date	Signature
Person writing the SAP	Martin Bækgaard Stisen	15/5/2024	
Senior statistician responsible	Erik Parner	15/5/2024	
Chief investigator/ Clinical lead	Inger Mechlenburg	15/5/2024	

Section 2: Introduction

Background and rationale

Revision total hip replacement (THR) is a common and serious complication after primary THR. In 2022, a total of 1,324 patients underwent revision THR in Denmark (1). Revision THR is commonly undertaken due to loosening, dislocation, fracture, or infection (2,3). Evidence on revision THR in terms of the effectiveness of pain relief and functional improvement is limited (4), and consensus on optimal rehabilitation after revision THR is yet to be established (5). Consequently, there is a need for research exploring different rehabilitation approaches to improve clinical outcomes for patients after revision THR.

Neuromuscular exercise (NEMEX) aims to enhance postural control and functional stability through functional exercises grounded on biomechanical and neuromuscular principles (6). Its effectiveness for reducing pain and improving physical function, and quality of life in hip osteoarthritis (OA) is well-documented (7-10). However, to our knowledge, the effects of postoperatively NEMEX remain unexplored in primary THR patients, as well as in the context of revision THR patients.

Patients with hip OA commonly present with decreased muscle mass and strength (11). These deficiencies persist after primary THR (12-14) and possibly will be even more reduced after revision THR. Notably, muscle strength correlates with functional performance in patients with hip OA (15). Progressive resistance training is considered the most effective intervention for increasing muscle mass and strength (16). Therefore, integrating a resistance training component (external resistance) into the NEMEX program to enhance hip muscle strength and function, seems warranted after revision THR.

Objectives

The primary objective of this RCT is to compare the effectiveness, four months after initiating rehabilitation, of an exercise intervention targeting hip strengthening (NEMEX-STR) with standard community-based rehabilitation (Usual care) on functional performance in patients undergoing revision THR.

A secondary objective is to compare the effectiveness, 12 months after initiating rehabilitation, on functional performance.

The primary hypothesis for the 4-month and 12-month comparison is that NEMEX-STR is superior to Usual care in functional performance, measured by the 30-second chair stand test (30s-CST).

Section 3: Study Methods

Trial design

The Strong Hip trial is a multicenter randomized controlled parallel-group assessor-blinded trial conducted across eight hospitals in Denmark, along with their affiliated municipality rehabilitation centers. Participants will be randomized to receive one of two rehabilitation interventions in a 1:1 ratio: either NEMEX-STR or Usual care. The primary outcome is change in functional performance, assessed by the 30s-CST, and the primary endpoint is four months after initiating the rehabilitation intervention. Outcomes will be measured at baseline, as well as at 4- and 12-month follow-ups. Detailed descriptions of the rehabilitation exercise protocols can be found in the trial protocol.

Reporting of the trial will follow the 'Consolidated Standards of Reporting Trials' (CONSORT) statement guidelines (17). This SAP is reported following the 'Guidelines for the Content of Statistical Analysis Plan in Clinical Trials' (18).

Randomization

Following their revision THR, patients are randomized in a 1:1 ratio to either NEMEX-STR or Usual care. Utilizing the Research Electronic Data Capture (REDCap) randomize tool, a computer-generated list of random numbers is generated (19). Randomization is stratified by the participating hospitals with block sizes selected randomly. Throughout the trial, block sizes and randomization sequences remain blinded for the administrator of the randomization procedure.

Sample size

The sample size calculation is based on the expected between-group difference in the 30s-CST from baseline to 4-month follow-up. Given the absence of revision THR-specific data, the calculation relies on primary hip and knee replacement studies, as well as data from patients with hip and knee OA. The major clinically important improvement for 30s-CST among hip OA patients is defined as 2.1 chair stands (20). Mikkelsen et al. (21) observed a mean change of 2.84 chair stands in patients undergoing primary THR following 10 weeks of supervised progressive resistance training in combination with unsupervised home-based exercise. Further, Abbott et al. (22) reported a mean change of 0.59 among patients with hip or knee OA at 1-year follow-up after receiving usual care. The standard deviation for the 30s-CST, obtained from the 95% CI of the change in the intervention group of the study by Mikkelsen et al. (21), is calculated as 3.03. With a significance level set at 5% and a sample size of 60 patients, the study will have 80% power to detect a change of 2.25 chair stands. Accounting

for loss to follow-up of 40%, determined in consideration of the complex population, the total sample size is 84 patients.

Framework

The overall objective of this trial is to ascertain whether NEMEX-STR results in a clinically and statistically significantly greater improvement compared to Usual care in the 30s-CST, Hip Disability and Osteoarthritis Outcome Score (HOOS), 40m Fast-paced Walk Test (40m-FPWT), 9-step Timed Stair Climb Test (9-step TSCT), Leg Extensor Power, Global perceived effect (GPE), Adverse events and serious adverse events, Adherence and drop-outs, The International Physical Activity Questionnaire (IPAQ), Numerical rating scale for pain (NRS), and European Quality of Life - 5 Dimensions (EQ-5D-5L). The primary hypothesis is that NEMEX-STR is superior to Usual care at 4 months, and the secondary hypothesis is that NEMEX-STR is superior to Usual care at 12 months.

Statistical interim analysis and stopping guidance

No formal statistical interim analysis is planned for the StrongHip Trial. Participant enrolment started in November 2022 and is expected to be completed by June 2024. All participants are expected to have completed 4-month follow-up assessments by February 2025, and 12-month follow-up assessments by October 2025.

Timing of final analysis

For the 4-month comparison, the final analysis is planned to be conducted when all randomized participants have completed the 4-month follow-up. The anticipated publication submission time is ultimo 2025. Likewise, for the 12-month comparison, the final analysis is planned when all randomized participants have completed the 12-month follow-up. The anticipated publication submission time is ultimo 2026.

Timing of outcome assessments

This trial entails outcome assessments at three time points; baseline, 4 months after initiation of the rehabilitation intervention, and 12 months after initiation of the rehabilitation intervention. An overview of the timing of outcome assessments is presented in Table 1.

Section 4: Statistical Principles

Confidence intervals and *P* values

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 with 95% confidence intervals.

Adherence and protocol deviations

For the NEMEX-STR group, adherence to exercise will be self-registered by the participants in an exercise log (supervised sessions will be registered by the physiotherapists supervising the exercise sessions). Adherence will be presented as descriptive statistics (numbers and percentages). Adherence percentage is calculated as the number of sessions completed divided by the number of sessions planned multiplied by 100%. High adherence for the 4 months is defined as attendance in ≥80% of the exercise sessions. Further, for the NEMEX-STR group, the proportion of patients reaching difficulty levels 1, 2, and 3 will be presented. Any protocol deviations, i.e., drop-outs, reoperation, or initiation of other exercise treatments, will also be presented as descriptive statistics (numbers and percentages).

Analysis populations

The primary analyses will follow the Intention-to-Treat (ITT) principle, encompassing all participants randomized to treatment in the analyses, irrespective of adherence or protocol deviations. Participants who drop out will contribute data to their respective allocation groups until they drop out, without any imputations made.

A secondary analysis will incorporate a per-protocol analysis, wherein per protocol is defined as patients complying with the assigned treatment.

Subsequent per-protocol analyses will be conducted, excluding patients with poor adherence to the exercise sessions in the NEMEX-STR intervention (<80% of the planned sessions), and participants in the Usual care intervention who deviate from the randomized treatment.

Section 5: Trial Population

Screening data

At each of the eight hospitals, eligible revision THR patients will be screened for the predetermined eligibility criteria. Patients meeting these criteria will be invited to participate. The count of patients

who does not meet the criteria and the reason for ineligibility will be documented in a CONSORT flow chart (Figure 1).

Eligibility

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

Inclusion criteria:

1. Undergoing first revision THR.
2. Age ≥18 years.
3. Acceptance to participate in an exercise program for 16 weeks.
4. Cup and/or stem replaced, or a combination of liner and caput replaced.
5. Able to perform baseline tests.

Exclusion criteria:

1. Dependency on a wheelchair.
2. Other preplanned lower limb surgery within 12 months.
3. Body Mass Index (BMI) score >40.
4. Currently undergoing cancer treatment, e.g., chemo-, immuno-, or radiotherapy.
5. Comorbidities that prevent exercise, e.g. stroke, significant heart diseases, or similar (Orthopedic surgeons and/or physiotherapists determine if a patient is unable to exercise during consultations or upon discovering comorbidities).
6. Inadequacy in written and spoken Danish.
7. Mentally unable to participate.

Recruitment

The CONSORT flowchart will present the total number of patients who were screened, excluded (with reasons), randomized, receiving allocated treatment, discontinued intervention (with reasons), lost to follow-up (with reasons), included in the ITT analysis, and included in the per-protocol analysis.

Withdrawal/follow-up

Participants are allowed to withdraw from the study at any time during the trial period. Withdrawn participants will be encouraged to complete outcome assessments even though they stop attending exercise sessions. Withdrawals will be categorized into two options; [1] complete withdrawal from

the trial without further outcome assessments, and [2] withdrawal from the exercise intervention while still attending outcomes assessments. The reason and timing of withdrawals and loss to follow-up will be outlined in the CONSORT flowchart.

Baseline participant characteristics

Baseline participant characteristics will be presented by randomization group as seen in Table 2, entailing the following information: Gender, age, height, weight, cohabiting status, educational level, employment status, number of comorbidities measured with the Charlson Comorbidity Index, analgesic use (type(s) and frequency), indication for revision THR, time since primary THR, indication for primary THR, and indication for revision THR. Continuous variables will be presented as either mean with standard deviation (SD) if normally distributed, or as median with interquartile range (IQR) if not normally distributed. For categorical variables, numbers and corresponding percentages will be presented.

Section 6: Analysis

Outcome definitions

Primary outcome

30s Chair Stand Test (30s-CST)

The primary outcome is between-group differences in change from baseline to 4 months in the 30s-CST, measured by the number of repetitions (20,23,24). The 30s-CST was selected as the primary outcome because it is an objective measure of lower-extremity muscle strength and functional performance, which is simply standardized between testers and test locations, and considered valid and reliable (20,25,26). The 30s-CST is recommended by the Osteoarthritis Research Society International (OARSI) as part of the minimum core set of performance-based tests of physical function in people diagnosed with hip OA or following joint replacement (27).

Given the absence of a minimal important change (MIC) established specifically for the 30s-CST for revision THR patients, we will calculate a trial-specific MIC by subtracting the mean score of participants who reported experiencing a ‘small but not important improvement’ in the Global Perceived Effect (GPE) from the mean score of those reporting an ‘important improvement’ in the GPE.

Secondary outcomes

Hip Disability and Osteoarthritis Outcome Score (HOOS)

As a secondary outcome measure, the study will examine the between-group differences in change from baseline to 4 and 12 months in the five separate subscales of the HOOS covering pain, symptoms, activity limitations daily living, sport and recreation function, and hip-related quality of life HOOS (28). Each subscale ranges from 0-100, worst to best (29). It is valid and reliable in patients undergoing THR (28,30,31).

The 40m Fast-paced Walk Test (40m-FPWT)

Another secondary outcome of interest is the between-group differences in change from baseline to 4 and 12 months in the 40m-FPWT, quantified in seconds. It is measured as the time it takes to walk a 10m walkway four times in total as quickly and as safely as possible (20,23). The 40m-FPWT is a valid measure of maximum walking speed over a short distance, exhibiting excellent reliability (20).

The 9-step Timed Stair Climb Test (9-step TSCT)

Another secondary outcome is the between-group differences in change from baseline to 4 and 12 months in the 9-step TSCT, measured in seconds (23,32). It is measured as the time it takes to ascend and descend a 9-step stair and has excellent reliability in patients with hip OA (20,33-35).

Nottingham Leg Extensor Power Rig (NLEPR)

Another secondary outcome is the between-group differences in change from baseline to 4 and 12 months in leg extensor muscle power (watt/kg), measured with the NLEPR. Leg extensor muscle power is highly correlated with functional performance (36-38), and the NLEPR has acceptable reliability in patients undergoing THR (33,39,40).

Global perceived effect (GPE)

Another secondary outcome is the proportion of participants in each treatment group experiencing an 'important improvement' at 4 and 12 months using the GPE. It will be assessed for three domains; pain, activities of daily living, and quality of life rated on a 7-point Likert scale (41,42).

Adverse events and serious adverse events

Adverse events (AE) and serious adverse events (SAE) will be continuously recorded throughout the trial and defined in accordance with the 'International Council on Harmonisation of Technical Re-

quirements for Pharmaceuticals for Human Use - Guideline for good clinical practice' (43,44). Physiotherapists supervising the exercise sessions will monitor the events, and patients will be asked about potential AE and SAE during follow-ups following recommendations from the CONSORT group.

Adherence and drop-outs

Exercise adherence and progression within the NEMEX-STR intervention will be documented by the supervising physiotherapist. Further, patients will maintain exercise logs, to monitor adherence to home-based sessions. Adherence is described in detail in the 'Adherence and protocol deviations' section.

Other outcomes

Physical activity

An other outcome of interest is physical activity assessed by the International Physical Activity Questionnaire (IPAQ), which is a 7-item questionnaire containing open-ended questions about the patient's last 7-day recall of physical activity (45,46).

Numerical rating scale for pain (NRS)

An other outcome is patient-reported pain intensity at rest rated using NRS, which is an 11-item scale ranging from 0 to 10, with 0 indicating no pain and 10 indicating the worst imaginable pain (47,48).

European Quality of Life - 5 Dimensions (EQ-5D-5L)

An other outcome is Health-Related Quality of Life evaluated through the EQ-5D-5L, a patient-reported instrument that encompasses five dimensions; mobility, self-care, usual daily activities, pain/discomfort, and anxiety/depression (49). Additionally, it includes a visual analog scale (VAS) to measure self-rated health. The EQ-5D-5L is a valid and reliable measure of HRQoL in patients undergoing primary THR (49-51).

Analysis methods

Between-group comparisons of changes from baseline to follow-up in both the primary and continuous secondary outcomes will be analyzed following the ITT principle (i.e., patients analyzed according to their initial randomization, irrespective of adherence or potential crossovers) using a mixed-effects model of baseline and follow-up measurements as outcome, but restricting the mean baseline measurement to be the same in the two randomization groups (52,53). Fixed effects will

encompass the treatment group and time point, allowing evaluation of the effects of both interventions and observing progression over time. To accommodate within-patient correlation and potential clustering effects, random effects for patients and hospital sites will be incorporated. Further, fixed covariates such as age and sex, will be included to minimize the residual variation.

Missing data

As stated prior, no imputations will be applied in the analysis. However, the mixed-effects model manages potential missing outcome data. Each randomized participant will be included in the ITT analysis with the data collected for that participant. An effort to collect data from all randomized participants will be made, regardless of their adherence to interventions.

Additional analysis

No additional analyses are planned for the 4- and 12-month follow-up.

Harms

Adverse events and serious adverse events will be presented as numbers and percentages for each event.

Statistical software

All statistical analyses will be conducted using Stata (StataCorp, College Station, Texas, USA).

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Figures and tables

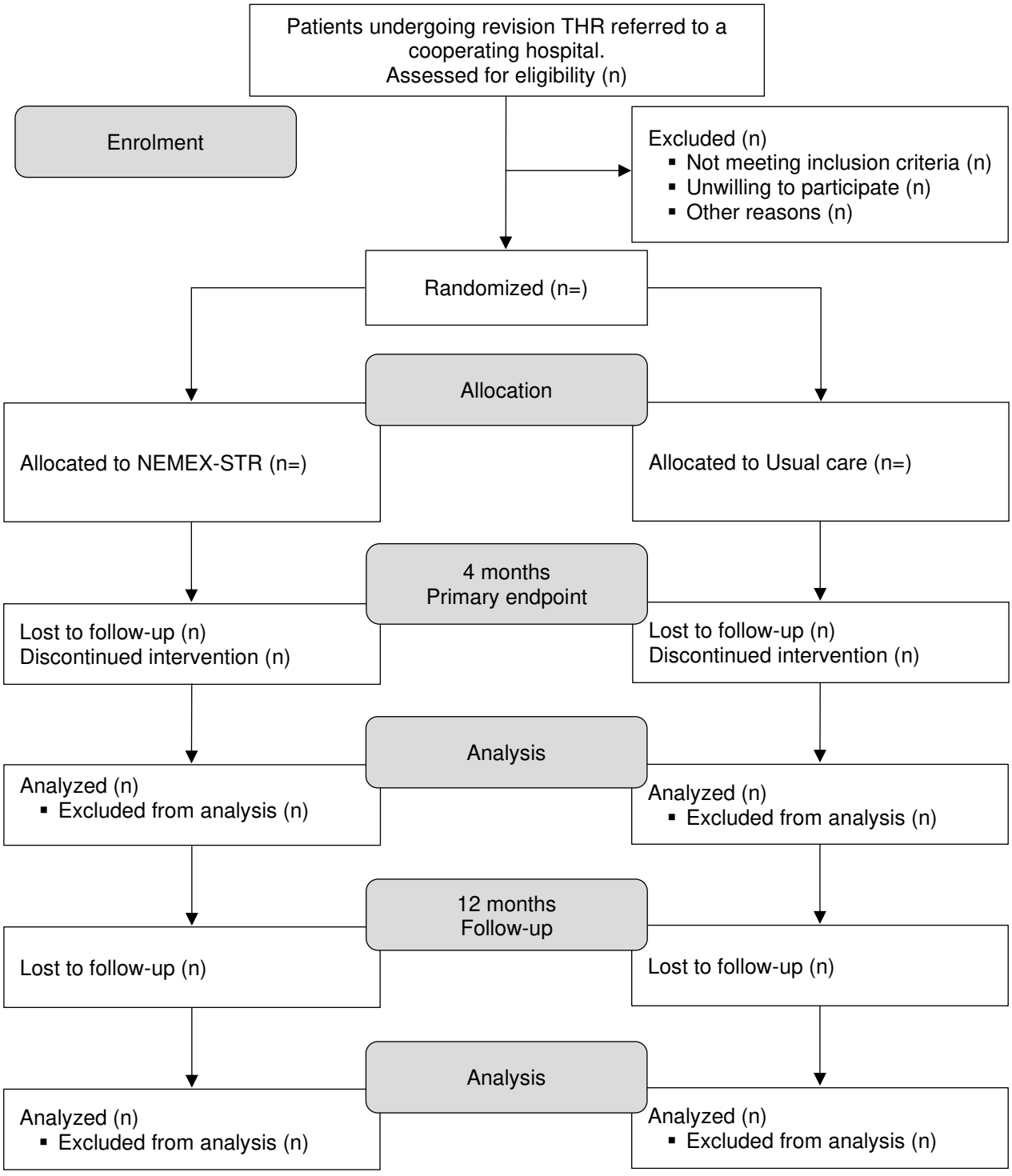

FIGURE 1. Flow chart with expected enrolment, randomization, and follow-up.
Abbreviations: THR, Total Hip Replacement; 30s-CST, 30-second Chair Stand Test.

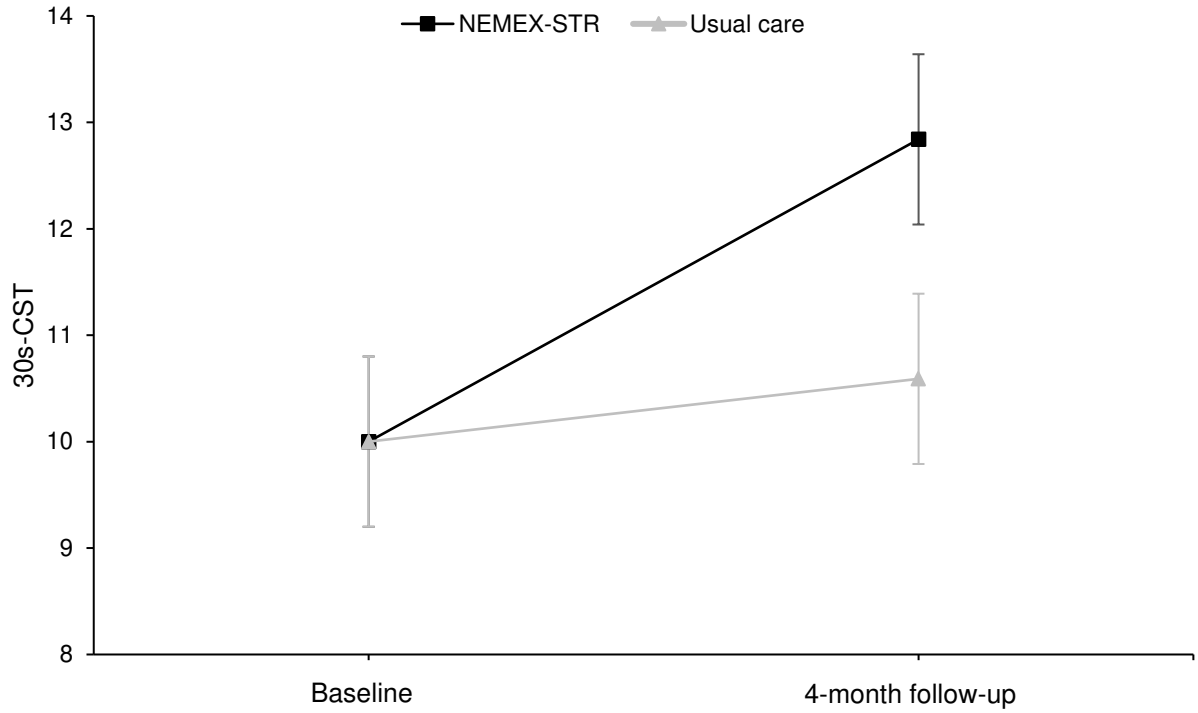

FIGURE 2. Change in 30-second chair stand test from baseline to 4-month follow-up. This figure is an example and displays the anticipated changes.
Abbreviations: 30s-CST, 30s Chair Stand Test.

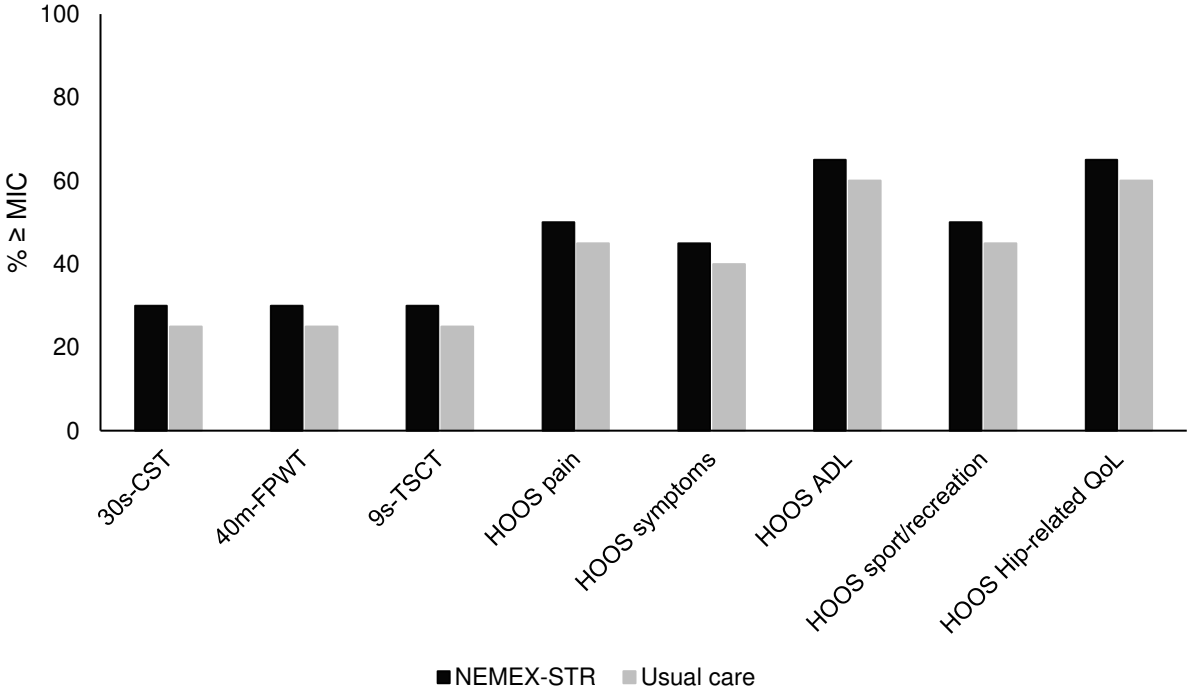

FIGURE 3. The proportion of participants reaching the clinically relevant improvement in primary and secondary outcomes. This figure is an example and displays the anticipated changes.
Abbreviations: MIC, Minimal Important Change; 30s-CST, 30s Chair Stand Test; 40m-FPWT, 40m Fast-paced Walk Test; 9-step TSCT, 9-step Timed Stair Climb Test; HOOS, Hip Disability and Osteoarthritis Outcome Score; ADL, Activity Limitations Daily Living; QoL, Quality of Life.

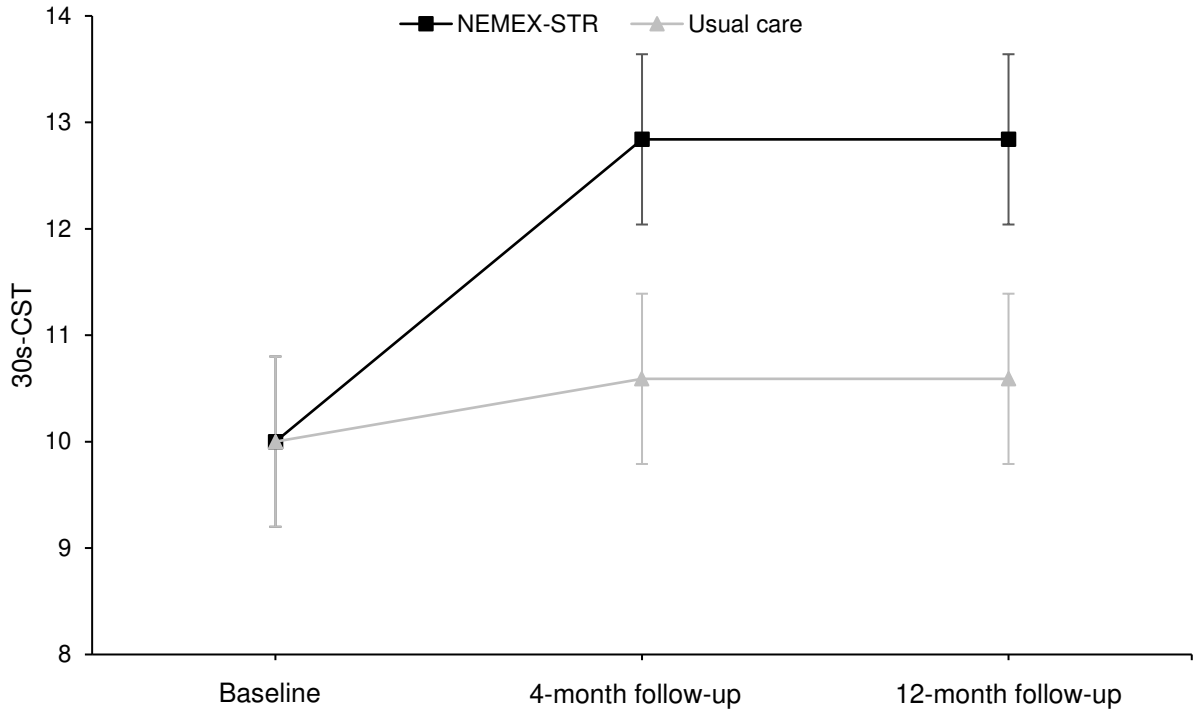

FIGURE 4. Change in 30-second chair stand test from baseline to 4- and 12-month follow-up. This figure is an example and displays the anticipated changes.
Abbreviations: 30s-CST, 30s Chair Stand Test.

TABLE 1. Table of outcome and baseline characteristics assessments

Assessments	Baseline	4 months	12 months
Primary outcome			
30s Chair Stand Test	X	X	X
Secondary outcomes			
HOOS	X	X	X
40m Fast-paced Walk Test	X	X	X
9-step Timed Stair Climb Test	X	X	X
Leg extension muscle power	X	X	X
Global perceived effect		X	X
Adverse events and serious adverse events		X	X
Adherence and drop-outs		X	
Other outcomes			
IPAQ	X	X	X
Pain (NRS)	X	X	X
EQ-5D-5L	X	X	X
Baseline characteristics			
Gender	X		
Age	X		
Height	X		
Weight	X		
Cohabiting status	X		
Highest obtained educational level	X		
Employment status	X		
Number of comorbidities	X		
Analgesic use	X		
Indication for revision THR	X		
Time since primary THR	X		
Indication for primary THR	X		

Abbreviations: HOOS, Hip Disability and Osteoarthritis Outcome Score; IPAQ, The International Physical Activity Questionnaires; NRS, Numeric Rating Scale; EQ-5D-5L, European Quality of Life - 5 Dimensions; THR, Total Hip Replacement.

TABLE 2. Baseline characteristics.

Characteristic	NEMEX-STR (n=)	Usual care (n=)
Gender, n(%)		
Female		
Male		
Mean age (SD), y		
Mean BMI (SD), kg/m^2		
Cohabiting status, n(%)		
Cohabiting		
Living alone		
Educational level, n(%)		
Primary school		
High school or similar		
Vocational education		
Higher education		
Employment status, n(%)		
Employed or self-employed		
Unemployed		
Retired		
Comorbidities (CCI), n(%)		
Low		
Medium		
High		
Analgesic use, n(%)		
Acetaminophen		
Nonsteroidal anti-inflammatory drugs		
Morphine or opioids		
Other		
Analgesic use frequency, n(%)		
Never		
Monthly		
Weekly		
Daily		
Indication for revision THR, n(%)		
Implant wear		
Loosening		
Dislocation or hip instability		
Pain		
Infection		
Fracture		
Other		
Time since primary THR (SD), y		
Indication for primary THR, n(%)		
Osteoarthritis		
Fracture		
Dislocation		
Other types of arthritis		
Congenital hip problems		
Other		

Abbreviations: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; THR, Total Hip Replacement

TABLE 3. Change from baseline to 4-month follow-up in primary and secondary outcomes.

	NEMEX-STR			Usual care			Difference in change
Intention to treat analysis							
	Baseline (SD)	**4-month (SD)**	**Change (CI)**	**Baseline (SD)**	**4-month (SD)**	**Change (CI)**	**Difference (CI)**
Functional performance							
30s-CST							
40m-FPWT							
9-step TSCT							
Leg Extension Power							
Patient-reported outcomes							
HOOS Symptoms							
HOOS Pain							
HOOS ADL							
HOOS Sport/recreation							
HOOS Hip-related QoL							
Per-protocol analysis							
	Baseline (SD)	**4-month (SD)**	**Change (CI)**	**Baseline (SD)**	**4-month (SD)**	**Change (CI)**	**Difference (CI)**
Functional performance							
30s-CST							
40m-FPWT							
9-step TSCT							
Leg Extension Power							
Patient-reported outcomes							
HOOS Symptoms							
HOOS Pain							
HOOS ADL							
HOOS Sport/recreation							
HOOS Hip-related QoL							

Abbreviations: 30s-CST, 30s Chair Stand Test; 40m-FPWT, 40m Fast-paced Walk Test; 9-step TSCT, 9-step Timed Stair Climb Test; HOOS, Hip Disability and Osteoarthritis Outcome Score; ADL, Activity Limitations Daily Living; QoL, Quality of Life.

TABLE 4. Serious adverse events, adverse events, drop-outs, and adherence to interventions at 4-month follow-up.

	NEMEX-STR	Usual care
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 (%)		
Mean adherence to exercise – (%)*		
≥ 80% adherence – n (%)		
≥ 50% adherence – n (%)		
< 50% adherence – n (%)		
Adherence to Usual care** – n (%)		

*Adherence to exercise; Number of patients in the NEMEX-STR group who participated in ≥ 80%, ≥ 50%, < 50% of exercise sessions.
**Adherence to Usual care; Number of patients in the Usual care group who followed the exercise regimen and didn't crossover to other exercise treatments.

TABLE 5. Change from baseline to 12-month follow-up in primary and secondary outcomes.

	NEMEX-STR			Usual care			Difference in change
Intention to treat analysis							
	Baseline (SD)	**12-month (SD)**	**Change (CI)**	**Baseline (SD)**	**12-month (SD)**	**Change (CI)**	**Difference (CI)**
Functional performance							
30s-CST							
40m-FPWT							
9-step TSCT							
Leg Extension Power							
Patient-reported outcomes							
HOOS Symptoms							
HOOS Pain							
HOOS ADL							
HOOS Sport/recreation							
HOOS Hip-related QoL							
Per-protocol analysis							
	Baseline (SD)	**12-month (SD)**	**Change (CI)**	**Baseline (SD)**	**12-month (SD)**	**Change (CI)**	**Difference (CI)**
Functional performance							
30s-CST							
40m-FPWT							
9-step TSCT							
Leg Extension Power							
Patient-reported outcomes							
HOOS Symptoms							
HOOS Pain							
HOOS ADL							
HOOS Sport/recreation							
HOOS Hip-related QoL							

Abbreviations: 30s-CST, 30s Chair Stand Test; 40m-FPWT, 40m Fast-paced Walk Test; 9-step TSCT, 9-step Timed Stair Climb Test; HOOS, Hip Disability and Osteoarthritis Outcome Score; ADL, Activity Limitations Daily Living; QoL, Quality of Life.

TABLE 6. Serious adverse events, adverse events, and drop-outs at 12-month follow-up.

	NEMEX-STR	Usual care
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 (%)		