Statistical analysis plan for the NEPNEP trial - A randomized controlled trial for chronic pain after primary total knee arthroplasty

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1.0

Section 1: Administrative information

Title and trial registration

Item 1a: Descriptive title

Statistical analysis plan for the NEPNEP trial – a randomized controlled trial for chronic pain after primary total knee arthroplasty.

Item 1b: Trial registration number

Trial registration: ClinicalTrials.gov: NCT03886259 (registered 22.03.2019)

Version

Item 2: Statistical analysis plan (SAP version number with dates

Statistical analysis plan version 1.0. Date: 17th January 2023

Protocol version

Item 3:

The SAP is based on the protocol approved by the North Denmark Region Committee on Health Research Ethics (N-20180046) and the study protocol which was published the 24.02.2020 (1). The SAP was made publicly available prior to the last participant has completed the 12-month follow-up and before commencing any analyses of the outcomes.

SAP revisions

Item 4a/b/c:

No revisions have been made

Roles and responsibilities

Item 5: Roles, affiliations, and SAP contributors

Principal investigator:

Jesper Bie Larsen, PT, PhD, Musculoskeletal Health and Implementation, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark

Study chair:

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Item 6a: Signature of person writing the SAP

Jesper Bie Larsen

Date: 17.01.2023

Item 6b: Signature of senior statistician responsible

NEB Skriv tekst her

Item 6c: Signature of chief investigator

Jesper Bie Larsen

Date: 17.01.2023

Section 2: Introduction

Background and rationale

Item 7:

Osteoarthritis is considered the most frequent cause of disability and pain in the elderly population, and the knee joint is one of the joints most commonly and severely affected(2,3). End-stage osteoarthritis is often treated with knee arthroplasty and primary total knee arthroplasty (TKA) is considered an effective treatment for pain relief and improved function(4,5). However, several studies have reported less favorable outcomes after primary TKA(6,7). Two systematic reviews found chronic pain rates after primary TKA of 13-17% among patients 12 months post-operatively and chronic pain rates at 2-7 years post-operatively varying between 8-27%(8,9). The causes of chronic pain after TKA remains largely unexplained(10). Signs of peripheral and central sensitization has been observed in chronic pain patients following TKA(10,11). The causes of chronic pain have been shown to be complex(12) and it has been suggested that the chronic pain in patients after TKA is predominantly centrally driven(10,11).

There is a lack of evidence-based treatments available for this group of patients. Therefore, this randomized controlled trial aims at investigating whether neuromuscular exercises combined with pain neuroscience education will provide superior results in terms of pain relief and improved physical performances compared to pain neuroscience education alone at 12-months follow-up.

Objectives

Item 8: Description of objectives and hypothesis

The objective is to evaluate whether a 12-week neuromuscular exercise program combined with pain neuroscience education is superior to pain neuroscience education alone in terms of improving pain and physical performances at 12-months follow-up in a population of patients with chronic pain after primary TKA.

Hypothesis:

We hypothesize that the patients randomized to neuromuscular exercise and pain neuroscience education will improve significantly more in pain and physical performances from baseline to 12-months than the patients randomized to pain neuroscience education alone.

Section 3: Trial methods

Trial design

Item 9: Description of trial design

This trial is designed as a randomized controlled superiority trial. Treatment allocation will be in a 1:1 ratio. The patients will be randomized to receive either neuromuscular exercises and pain neuroscience education or pain neuroscience education alone(1). The primary endpoint is at 12-months follow-up and a secondary endpoint, consisting of long-term follow-up, at 24-months.

Randomization

Item 10: Randomization details

The randomization was performed using computer-generated random numbers in permuted blocks of four to eight patients. After informed consent and baseline assessment had been conducted, the principal investigator randomly assigned patients to either of the treatment arms based on the computer-generated randomization. Thereafter, the allocation was provided to the patients.

The outcome assessors are blinded to the group allocation, are not a part of the provided interventions and are not affiliated with any of the treatment sites. Patients and physiotherapists providing the interventions cannot be blinded towards randomization.

Sample size

Item 11: Full details of sample size calculation

For $KOOS_4$ and KOOS scores, a minimal clinically important difference of 10 is estimated, and commonly used(13). A sample size calculation was conducted to estimate how large a sample size is required to give the study a power of 90% to detect a minimum improvement of 10-point on the $KOOS_4$, after 12 months follow-up, in the neuromuscular exercise and pain neuroscience education

group compared with the pain neuroscience education alone group (with a standard deviation of 15)(13,14). A two-sided significance level at 0.05 was set and results revealed that 49 patients are required in both groups. To account for possible missing data and a loss to follow-up of 20%, a total of 60 patients in each group was planned to be enrolled.

However, this study was impacted by the COVID-19 pandemic making recruitment particularly difficult and causing higher dropout rate than originally anticipated. Therefore, we were not able to recruit as many participants as planned and we decided to stop the trial early after recruiting for 44 months. Therefore, a total of 71 patients have been enrolled with 36 patients in the neuromuscular exercise and pain neuroscience education group and 35 patients in the pain neuroscience education alone group.

Framework

Item 12: Description og hypothesis testing framework

All outcomes, i.e., primary, secondary, and other outcomes, will be evaluated in a superiority framework, hypothesizing that the patients receiving neuromuscular exercises and pain neuroscience education will improve more than patients receiving pain neuroscience education alone. A confidence interval including 10 points or more in the $KOOS_4$ score will be interpreted as a clinical meaningful difference, although we will interpret results with caution given the fact that we did not reach the target sample size.

Statistical interim analysis and stopping guidance

Item 13:

No interim analysis was planned, and no adjustment of significance level was made. No stopping rules was defined a priory.

Timing of final analysis

Item 14:

The analysis of primary, secondary, and other outcomes will be conducted collectively when all patients have reached the 12-month follow-up. The 12-month follow-up is expected to be finished in March 2023. An independent statistician (NHB) will conduct the analysis. Data from all time points (baseline, 3-, 6-, and 12-months) will be included in the analysis.

The analysis of the primary, pre-specified secondary and other outcomes (presented in item 26 and table 2) will be reported in the primary 12-month follow-up publication. Remaining secondary outcomes will be reported in subsequent, secondary publications.

Evaluation of long-term outcomes based on baseline to 24-months (including baseline, 3-, 6-, 12-, and 24-months) follow-up will be conducted when all patients have reached the secondary endpoint at 24-month follow-up and this data collection has ended.

Timing of outcome assessments

Item 15:

All primary, secondary, and other outcomes will be evaluated at baseline, 3-, 6-, 12-, and 24-months, except for adverse events and adherence to interventions, which will be evaluated continuously during the intervention period and at 3-months, i.e., after the interventions have stopped. Further details can be found in the published study protocol(1)

Section 4: Statistical principles:

Confidence intervals and p-values

Item 16: Level of statistical significance

All conducted statistical tests will be two-sided and will be evaluated by a significance level of 5% (i.e., p= 0.05).

Item 17: Description of planned adjustment for multiplicity

The NEPNEP trial has one clearly specified primary outcome and the secondary and other outcomes will serve as supportive and/or hypothesis generating, which is why multiplicity is not considered to be an issue (15).

Item 18: Confidence intervals

The presented confidence intervals will 95% and be two-sided.

Adherence and protocol deviation

Item 19a: Definition of adherence to interventions

Adherence will be defined as participation in both pain neuroscience education sessions (valid for both groups). For the patients receiving neuromuscular exercises, adherence will be defined as participation in minimum 75% of the neuromuscular exercise sessions (i.e., 18 out of 24 exercise sessions). Adherence is registered by the physical therapists in charge of the neuromuscular exercise sessions and the pain neuroscience education sessions.

Item 19b: Description of how adherence to interventions will be presented

Adherence, for those randomized to neuromuscular exercise and pain neuroscience education, will be reported as the numbers and percentages of patients participating in at least 18 neuromuscular exercise sessions and participating in both pain neuroscience education sessions. Adherence, for those randomized to pain neuroscience education alone, will be reported as numbers and percentages of patients participating in both pain neuroscience education sessions.

Item 19c & 19d: Definition of protocol violation for the trial and how they will be presented

It is specified as an exclusion criterion if patients experience chronic pain due to loosening of implant or prosthesis failure which requires revision surgery. However, during the follow-up, patients might be referred to revision TKA surgery, e.g., based on new available information to the surgeon. Therefore, undergoing revision TKA during follow-up is defined as a major protocol

deviation, which could impact the outcomes of the trial. Number of patients in both randomized groups will be reported.

Analysis populations

Item 20: Definition of analysis populations

All outcomes will be analyzed according to the intention-to-treat principles. The intention-to-treat population will be all subjects randomized to either group. A per-protocol analysis will be conducted based on patient adherence to interventions. Therefore, the following will be excluded from the per-protocol analysis: 1) The patients who did not participate in both pain neuroscience education sessions, 2) The patients in the neuromuscular exercises and pain neuroscience education group participating in below 75% (18 out of 24) of the neuromuscular exercise sessions and 3) patients receiving revision surgery at any time-point during follow-up.

Section 5: Trial population

Screening data

Item 21: Reporting of screening data

The recruitment period, from start date to end date, will be displayed as well as the total numbers of patients screened for eligibility throughout the recruitment period.

Eligibility

Item 22: Summary of eligibility criteria

Patients were eligible to participate in the trial if they fulfilled the inclusion criteria:

- Male or female aged 40-80 years
- Body Mass Index (BMI) between 19-40 kg/m^2
- Subjects with pain after primary TKA and ≥ 12 months post-operative
- For the index knee, duration of knee pain > 6 months.
- For the index knee, a perceived average daily pain score ≥ 4 (moderate-to-severe pain) over the last week prior to recruitment on a numerical rating scale (NRS, 0 (no pain) to 10 (maximum pain)).

Study exclusion criteria were:

- chronic pain due to loosening of implant or prosthesis failure requiring revision surgery
- secondary causes of arthritis to the knee, such as rheumatoid arthritis or sequelae from previous accidents
- surgery (including arthroscopy) of the index knee within three months prior to recruitment
- injury to the index knee within 12 months prior to visit
- acute pain, other than in the index knee, affecting the lower limb and/or trunk at the time of baseline testing
- participation in other pain trials two weeks prior to recruitment
- pregnancy
- drug and alcohol abuse

- rheumatoid arthritis, neurologic illnesses, or primary pain area other than knee (e.g., low back pain or upper extremity pain)
- lack of ability to adhere to protocol

Recruitment

Item 23 & 24: Information to be included in CONSORT flow diagram

A CONSORT flow diagram will be displayed, including the following information:

- Number of patients assessed for eligibility throughout the recruitment period
- Number of patients not meeting the inclusion criteria's or not consenting to participate
- Number of patients eligible for inclusion
- Number of patients randomized to both treatment arms
- Number of patients with follow-up assessment at 3-, 6-, 12-months for the primary analysis of 12-months follow-up[1]
- Number of patients with follow-up assessment at 3-, 6-, 12-, 24-months for the secondary long-term analysis of 24-months follow-up[1]
- Number of withdrawals or loss-to-follow-up for each timepoint and reasons for withdrawal or loss-to-follow-up
- Number of patients included in the intention-to-treat analysis and the per-protocol analysis

Baseline patient characteristics

Item 25a: List of baseline characteristics to be summarized

Patients will be described with baseline, demographic characteristics which include age, sex, height, body mass, BMI, average daily pain intensity over last week, index knee, dominant leg, time-since-TKA-surgery, TKA in non-index knee, comorbidities, and scores on the Hospital Anxiety and Depression Scale(16). The following comorbidities will be recorded: Osteoarthritis in other areas than the index knee, chronic pain from other sites than the index knee, chronic obstructive pulmonary disease, diabetes, and cardiovascular disease. Comorbidities will be registered using the medical journals.

Item 25b: Details on how baseline characteristics will be descriptively summarized

Table 1 illustrates how the baseline characteristics will be presented. Continuous data will be presented as mean and SD if data is normal distributed and as median and range if data is non-normal distributed. Categorical data will be presented as numbers and percentages. No test for statistical significance for the baseline characteristics will be conducted in line with recommendations by the CONSORT statement (17). Instead, the clinical importance of any imbalances will be considered.

[1] Number of patients with follow-up assessment is defined as patients with data available for the primary outcome ($KOOS_4$). This will be displayed for each follow-up for both randomized groups.

Table 1: Patient baseline characteristics:

Characteristics	Neuromuscular exercise and pain neuroscience education group	Pain neuroscience education alone group
Age (years), mean (SD)		
Sex (men/women, n, %)		
Height (cm), mean (SD)		
Body mass (kg), mean (SD)		
Body mass index (kg/m^2), mean (SD)		
Average daily pain intensity over last week (numerical rating scale), mean (SD)		
Index knee (left/right, n, %)		
Dominant leg (left/right, n, %)		
Time since surgery (months), mean (SD)		
Total knee arthroplasty in non-index knee (yes/no, n, %)		
Comorbidities* (n, %)		
The Hospital Anxiety and Depression Scale (0-21), mean (SD)		

* The following comorbidities will be recorded: Osteoarthritis in other areas than the index knee, chronic pain from other sites than the index knee, chronic obstructive pulmonary disease, diabetes, and cardiovascular disease.

Section 6: Analysis

Outcome definitions

Item 26: Specification of outcome and timings

Table 2 specifies which outcomes are collected, the timepoints for their assessment and the analysis methods. Further details can be found in the open access protocol (1).

Table 2: Overview of primary, secondary and other outcomes. For more details, please refer to the open access protocol (1)

	Instrument for assessment	Timing of assessment	Analysis method
Primary outcome – reported in primary publication			

$KOOS_4$, mean value of four KOOS subscales scores	KOOS subscales pain, symptoms, activities of daily living and knee-related quality of life Each question in KOOS is assigned a score from 0 to 4 and a normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. The $KOOS_4$ subscales scores are aggregated and averaged as the primary outcome	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Secondary outcomes – reported in primary publication			
KOOS	All KOOS subscales, i.e., pain, symptoms, activity of daily living, sport/recreation and knee-related quality of life are individually reported	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Global Perceived Effect	Questionnaire	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
40-meter fast-paced walk test	Time to complete the 40-meter walking test and calculation of walking speed (meters/second)	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Stair climb test	Time to complete the stair climb test	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
30-second chair stand test	Number of chair stands in the 30sec. chair stand test	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Usage of pain medication	Patient self-report of usage of pain medication during last week registered as yes/no. Registration of the number of Paracetamols (1 gram) and Ibuprofen and other non-steroidal anti-inflammatory drugs (400 mg.). If any additional pain medication was used, this will be registered as well	Baseline, 3-, 6-, 12-, and 24-months	Poisson regression model
Other outcome – reported in primary publication			
Adverse events	Number of adverse events self-reported by the patients and observed by the physiotherapists supervising the interventions	Continuously during the intervention period	Poisson regression model
Hospital Anxiety and Depression Scale	Questionnaire. Reported as a baseline characteristic	Baseline	No statistical analysis
Other treatments received	Patient self-report of other types of treatment received, defined as treatments that the patient had initiated because of the index knee (e.g., acupuncture, manual therapy, surgery, physiotherapy)	Baseline, 3-, 6-, 12-, and 24-months	Poisson regression model
Secondary outcomes – reported in secondary publications			

PainDETECT	Questionnaire	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Fear-avoidance Beliefs Questionnaire – Physical Activity	Questionnaire	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Pain Catastrophizing Scale	Questionnaire	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Pain intensity in various situations	Average daily pain intensity over the last week, maximal pain intensity during rest (day and night), stair climbing, and walking using a numerical rating scale	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Pain location	Number of painful sites concerning habitual pain areas using a pain drawing on an anatomical body chart	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Pressure pain thresholds	Measured using a handheld algometer (Somedic, Hörby Sweden) locally at the index knee and extrasegmentally at the forearm	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Conditioned pain modulation	Measured using pressure pain threshold as test stimuli and a spring-based pressure clamp as conditioning stimuli	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Pinprick hyperalgesia	Measured locally at the index knee and extrasegmentally at the forearm using a pinprick nylon filament (Chicago Medical Supply)	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Temporal summation	Measured locally at the index knee and extrasegmentally at the forearm using a pinprick nylon filament (Chicago Medical Supply)	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Dynamic mechanic allodynia	Measured locally at the index knee and extrasegmentally at the forearm using a cotton swab	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Deep somatic hyperalgesia	Measured locally at the index knee and extrasegmentally at the forearm using a pressure algometer (syringe)	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Maximal leg extension power	Measured in Watt using a leg extension power rig (Nottingham power rig, Nottingham, UK) for index and non-index knee	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model
Maximal isometric muscle strength of knee extensors and flexors	Measured in Newton using a handheld dynamometer (Lafayette Manual Muscle Tester, Loughborough, UK or MicroFET2, Hoggan Scientific, LLC, Salt Lake City UT, USA Calculation of isometric hamstring/quadriceps (H/Q) ratio for index and non-index knee using the formula “isometric hamstring strength	Baseline, 3-, 6-, 12-, and 24-months	Repeated measures mixed model

	divided with isometric quadriceps strength = H/Q ratio”		

KOOS: Knee injury and Osteoarthritis Outcome Score.

Analysis methods

Item 27:

Primary, pre-specified secondary and other outcomes presented in table 2 will be reported in the primary 12-month follow-up publication. The same outcomes will be presented for the secondary publication of long-term follow-up when the 24-month data collection is completed (approximately March 2024). Remaining secondary outcomes presented in table 2 will be presented in subsequent, secondary publications.

The primary outcome will be the between-group change in $KOOS_4$ from baseline to 12-month follow-up. Statistical tests will be dependent on data distribution. Validation of normal distribution will be done by reviewing data frequency in histograms and tests for normality (Shapiro-Wilk). For continuous outcomes, we expect data to be normally distributed, and therefore, will be using a repeated measures mixed model with patients as random effect and visit (baseline, 3-, 6-, 12-months) and treatment arm (neuromuscular exercises and pain neuroscience education or pain neuroscience education alone) as fixed effects, and with adjustment for baseline imbalance. Interaction between follow-up and treatment arm was also included in the models. Both crude and adjusted values will be reported.

Secondary outcomes will be analyzed like the primary outcome as well as the long-term (24-month) follow-up analysis. Frequency of adverse events and other types of treatment received (see table 2) will be compared between-groups at the 12-months follow-up using a Poisson regression model with a robust error variance(18). Similarly, between-group comparison of relative risks concerning usage of pain medication will be analyzed using a Poisson regression model, with robust error variance.

A confidence interval including 10 points or more for the primary outcome $KOOS_4$ will be interpreted as a clinical meaningful difference.

A responder analysis, illustrating the proportion of patients in each randomized group that experienced a minimal clinically important improvement (i.e., minimum improvement of 10 points) for the primary outcome $KOOS_4$, will be made to evaluate between-group difference baseline to 12-months follow-up. Results will be analyzed using a Chi-squared test.

A figure including data from all time points (baseline, 3-, 6-, and 12-months) will be presented to visualize the mean value and 95% CI over time in $KOOS_4$ for the patients randomized to either neuromuscular exercise and pain neuroscience education or pain neuroscience education alone. A similar figure will be displayed for the secondary, long-term (24-months) follow-up analysis including all time points (baseline, 3-, 6-, 12-, and 24-months)

The patient’s individual trajectory of pain (illustrated by the KOOS pain subscale) and physical performance (illustrated by the 40-meter fast-paced walk test) will be depicted in graphs for both

randomized groups in the subsequent, secondary 12-months follow-up publications and for the secondary long-term (24-month) follow-up publication.

Missing data:

Item 28:

Since the linear mixed effects models includes all patients when at least the baseline value or a follow-up value is present, no imputation will be required(19,20). Number of data points available in each group at baseline, 3-, 6-, and 12-months will be displayed in primary and secondary publications. Number of data points available in each group at baseline, 3-, 6-, 12-, and 24-months will be displayed in in the secondary long-term follow-up (24-months) publication.

Additional analyses

Item 29:

Exploratory analyses of associations between pre-specified outcomes are planned and will be reported in secondary publications.

Multivariate linear regression models based on the enter method with an adjustment for age, sex, and BMI will be conducted to analyze associations between the primary outcome ($KOOS_4$) and pain-related outcomes, bedside quantitative sensory testing outcomes and physical performance outcomes. Two regression models will be conducted. One will include $KOOS_4$ as the dependent variable and leg extension power and maximal isometric muscle strength for knee flexors and extensor as independent variables and one will include $KOOS_4$ as the dependent variable and pressure pain thresholds, temporal summation, the fear-avoidance beliefs questionnaire and the pain catastrophizing questionnaire as independent variables.

An exploratory analysis is planned and will be reported in a secondary publication. All patients will be stratified according to their conditioned pain modulation responses, i.e., classified as a conditioned pain modulation responder, a conditioned pain modulation non-responder or no change in conditioned pain modulation. Further details for the stratification are described in the study *Larsen et al. Stratification of facilitatory or inhibitory conditioned pain modulation responses in patients with chronic knee pain. Explorative analysis from a multicenter trial (under review at European Journal of Pain).* Following stratification, data will be analyzed like the primary analysis (item 27). This analysis will allow us to verify if the treatment effect for the primary and secondary outcomes at 12-months is associated with conditioned pain modulation responses. Results will be presented with a figure including all data points (baseline, 3-, 6-, and 12-months) to visualize the mean and 95% CI over time for the primary outcomes $KOOS_4$ for each randomized group, stratified according to the conditioned pain modulation responses.

Further exploratory analyses can be conducted if deemed relevant.

Harms

Item 30: Sufficient detail provided on summarizing harms

Adverse events that may have occurred during the trial period will be identified by the patients (self-reported) and by the physiotherapists supervising the interventions (observations) (see table 3).

Adverse events are characterized as occurring in either the index knee or sites other than the index knee and serious events are defined according to the definitions from the U.S. Food and Drug Administration(21). Adverse events will be descriptively summarized for each randomized group similar to table 3 and be reported in the primary 12-months follow-up publication.

Table 3: Adverse events. The table will include all serious and non-serious adverse events that were registered during the 12-month follow-up period. Serious adverse events associated with the interventions is defined as events that result in death, a life-threating condition, hospitalization, disability or permanent damage, or other serious events, that does not fit the other outcomes (21).

Adverse events	**Neuromuscular exercise and pain neuroscience education group**	**Pain neuroscience education alone group**
	Number of events	
Serious events		
Site other than index knee:		
XXXX		
XXXX		
XXXX		
Index knee:		
XXXX		
XXXX		
XXXX		
All serious events		
Non-serious events*		
Sites other than index knee		
XXXX		
XXXX		
XXXX		
Index knee		
XXXX		
XXXX		
XXXX		
All non-serious		

events		

* Non-serious adverse events could be, but not limited to, increased pain in index knee, swelling of index knee, decreased range of motion, distortion of joints, musculoskeletal pain.

Statistical software

Item 31: Details of statistical package used for the analysis

The statistical package StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC was used for data management and analysis. The packages basetable and matrixtools were also used.

References

Item 32: Data management

The project is approved by The Danish Data Protection Agency (Aalborg University, 2018-899/10-0166). Data are stored in accordance with the stipulations in The Danish Personal Data Protection Act and other relevant Danish legislation. Data was recorded in hard copy during the outcome assessments and thereafter noted in Excel spreadsheets. Data entry and coding of the non-personal information will be administered by trained staff from Aalborg University. The main data set will not contain any personal information. No personal information will be shared outside the study group. All data, including hard copy data from the individual outcome assessment of the patients, will be stored securely.

The analyses described in this SAP will be the basis of all primary and secondary endpoints. Analyses will be made by the same independent statistician. The principal investigator will code the randomized groups in “group A” and “group B” before submitting the dataset to the statistician. Thereby, analyses will be blinded towards treatment allocation. First, the dataset will be provided for the statistician without information of adherence or adverse events to avoid that blinding is broken. Following finalization and reporting of the intention-to-treat analysis, the statistician will be given information on adherence and adverse events to conduct the per-protocol analysis.

To avoid the risk of misleading interpretation, the blinded results from the intention-to-treat analysis (group A vs. group B) will be presented to all authors. The author group will then decide on two different interpretations of the results, one in which group A refer to neuromuscular exercises and pain neuroscience education, and one in which group A refer to pain neuroscience education alone. The interpretations will be registered in a document titled “NEPNEP trial: Blinded data analyses statement of interpretation”. Following written registration and agreeing that no further changes will be made, the randomization code is broken, and the correct interpretation can be chosen(22).

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