Statistical Analysis Plan for *Keeping It Simple Study (KISS) – Pain science education for patients with chronic musculoskeletal pain undergoing community-based rehabilitation: A multicenter Randomized Controlled Trial.*

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Publication date:

December 20th, 2024

Document version:

1.0

Clinical Trials registration:

ClinicalTials.gov: NCT06297447 (Registered February 29th, 2024)

Ethical approval:

North Denmark Research Committee on Health Research Ethics and was evaluated and deemed except from needing approval (N-20230073). The AAU Research Ethics Committee has approved the research activity, Case No.: 2024-505-00157 on February 16th, 2024.

Funding:

This project is funded by *Karen Elise Jensen Fonden*, *Helsefonden* (**Grant no. 23-B-0275)**, *Danske Fysioterapeuter* **(A1430)** and *Køge Municipality*.

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Section 1: Administrative Information

Title and trial registration

Statistical Analysis Plan for *Keeping It Simple Study (KISS) – Pain science education for patients with chronic musculoskeletal pain undergoing community-based rehabilitation: A multicenter Randomized Controlled Trial.*

ClinicalTials.gov: NCT06297447 (Registered February 29th, 2024)

SAP Version

Statistical analysis plan version 1.0, December 20th, 2024

Protocol Version

The SAP is based on the protocol vers.1 uploaded to ClinicalTrials.gov on March 6th, 2024. The protocol was submitted to the North Denmark Research Committee on Health Research Ethics and was evaluated and deemed except from needing approval (N-20230073). The AAU Research Ethics Committee has approved the research activity, Case No.: 2024-505-00157 on February 16th, 2024.

SAP revisions

No revisions have been made.

Roles and responsibilities

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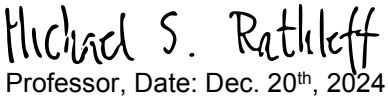
Chief Investigator, Date: Dec. 20th, 2024.



Professor, Date: Dec. 20th, 2024

Section 2: Introduction

Background and rationale

More than 20% of people across the globe live with chronic musculoskeletal pain (1) and have a high usage of health care and loss of productivity (2–4). Guidelines recommend pain science education (PSE) as an important part of care (5–9), however there are barriers to implementing this in real life context, including training of those delivering the PSE (10) and low levels of health literacy among patients (11). The investigators adapted a PSE program, originally intended for children, to Danish adults in a municipality rehabilitation setting (*Eiger, Rathleff et al. 2024 – under review*). The adapted version, named PNE4Adults, shows promise in facilitating patient's own understanding and management of pain, and was well accepted (*Eiger, Rathleff et al. 2024 – under review*).

As we in this very pragmatic trial (as evaluated on the PRECIS-2 tool (12)), have included all adults patients with chronic musculoskeletal pain referred for rehabilitation, it would be beneficial to examine if there are factors moderating the effect of the intervention, to be able to inform clinical practice on whom to deliver the intervention to, if any. Pre-selecting potential moderators and stating a priori direction for the expected direction is recommended (13). We plan to examine the interaction between treatment effect and baseline measures of potential effect modifiers (moderator analysis).

Objectives

The primary aim of the KISS-project is to evaluate the effect (as measured by MSK-HQ after three months) of PSE ('PNE4Adults') integrated into "usual care" compared to "usual care" alone in community-based rehabilitation.

H_A: The hypothesis is PSE integrated into "usual care" will result in a larger improvement of musculoskeletal health (MSK-HQ) after three months (primary endpoint) compared to patients undergoing "usual care" in the municipality.

Secondary aims:

1. To evaluate the effect of PSE ('PNE4Adults' integrated into "usual care") compared to "usual care" alone in community-based rehabilitation on the secondary outcomes (defined below) at three months (primary endpoint)

2. To evaluate the moderating effect of self-reported baseline Health literacy (B-HLA), Pain self-efficacy (PSEQ), Sensitization (CSI), and Pain Knowledge (COPI-Adult(DK)) on the effect of PSE (i.e., PNE4Adults + "usual care") compared to control (i.e., "usual care" alone) on changes in musculoskeletal health (primary outcome) at three months (primary end-point), as well as the moderating effect of baseline Health literacy(B-HLA) on changes in pain knowledge (COPI-Adult) and Pain self-efficacy (PSEQ) at three months.

Section 3: Study Methods

Trial design

This study is a multicenter randomized controlled, superiority trial with a 2-group parallel design. Patients will be allocated (1:1) into either control or intervention group. Preparation of this trial was done in accordance with the PREPARE Trial guide (14), and reporting of the protocol follows the SPIRIT statement (15) and the TIDier

guide (16) and the statistical analysis plan (SAP) follows the structure proposed by Gamble et al. 2017 (17). The study protocol was registered before inclusion of the first patient on clinicaltrials.org (NCT06297447) and the SAP is uploaded before the last patient is included.

Control group:

The control group receives unrestricted "usual care". It could include a patient interview with individual goal setting and subsequent rehabilitation using cardio and strengthening exercises towards achieving the determined goals. It will be delivered by an authorized physiotherapist (not the same as delivers the intervention), and the intervention is determined by patient preferences, physiotherapist's clinical reasoning, and available resources. It can be individual or group sessions, depending on patient needs and available resources. Control group is kept separate from "intervention group" and serviced by a separate group of physiotherapists.

Intervention:

In the intervention group, the participants will receive individualized PSE in addition to the "usual care" with the PNE4Adults resource. The PNE4Adults sessions will follow the developed manual (http://www.paininmotion.be/pne4kids) and will be delivered by a physiotherapist in two individual sessions of each 30-45 minutes, shortly following the first meeting. Firstly, the function of a normal pain system is introduced, with examples of the pain being overly or under protective. Then, the patient teaches back giving the therapist the opportunity to evaluate the understanding and, if necessary, repeat essential key messages. Secondly, the sensitized pain system is explained. Thirdly, the subject is asked to reflect on this new information in relation to his/her own situation. Subsequently, the new pain science knowledge is integrated into "usual care" with any additional measures that need to be included, e.g., graded exposure, stress relief, graded activity, and cognitive therapies. The "usual care" component can be delivered as individual or group sessions depending on patient needs and available resources. Intervention group is kept separate from "control" group to eliminate contamination. There are nine physiotherapists delivering the intervention. Four in Køge Municipality, three in Holbæk Municipality and two in Solrød Municipality. They have all received training in delivering the intervention, as described in the protocol.

Randomization:

Allocation
After filling out informed consent and baseline questionnaires, participants will be automatically randomized using REDCap. Randomization will be stratified by site. Block randomization in random permuted, concealed block sizes of 4 to 12 (1:1) into two parallel groups is used to avoid imbalance in the randomization between intervention groups. A researcher, not otherwise affiliated with the study will generate the allocation sequence using sealedenvelope.com and upload it to REDCap and is the only person who will know the block sizes and group code.

The randomization will be coded (Group 1 or 2), thus the primary investigator (BE) and other data analysist will not know the code to the groups.

Blinding
As patients are engaging in a behavioral intervention, they are not blind to allocation, and neither are the physiotherapists delivering the intervention/ usual care. Treatment expectation is measured after randomization by a single tailored question: *"How confident are you that this treatment option will be successful in improving your MSK pain"?* with the answer options being *"Very sure", "Sure", "Neither sure nor unsure", "unsure", "Very unsure".* The person conducting the analysis and primary investigator (BE) will remain blinded. The intervention is an add-on to "usual care". Pragmatically, there are no restrictions to

"usual care" in either group. It is determined by patient preferences, physiotherapists' clinical reasoning, and available resources in the municipalities.

Sample size.

The sample size calculation can be seen in the Protocol (ClinicalTials.gov: NCT06297447).

"The sample size calculation was performed using Stata vers. 16.0 and is based on our feasibility study and done in collaboration with a statistician. Our estimate of a sample size is based on the ability to detect a clinically relevant difference in MSK-HQ of 8.6 points between the two groups (18). To estimate a difference of 8.6 points (18), with a common standard deviation of 15 points, a two-sides type I error rate of 0.05, and a power of 95%, the sample size was estimated as 49 participants per group. Considering an attrition rate of 15% and a potentially larger variation than previous studies due to heterogeneity of participants, this requires 70 participants per group. The investigators anticipate that a sample-size of 70 participants per group will be sufficient to test for clinically meaningful differences between groups and ensure statistical power even if the variance in the outcome is larger than anticipated for the primary analysis. To allow for explorative subgroup analyses on the interaction of health literacy, the investigators will increase this sample-size to 100 patients per arm".

Framework

A superiority framework will be applied to evaluating all outcomes, i.e., primary, and secondary outcomes, hypothesizing that the patients in the intervention group will improve more than the patients in the control group.

Statistical interim analyses and stopping guidance.

None were planned.

No stopping rule was determined a priori as we don't expect any adverse events.

Timing of final analysis

The between-group analysis of primary and secondary outcomes will be conducted when all patients have reached the 6-month follow-up. The 6-month follow-up is expected to be finished in December 2025. An analyst blinded to the grouping variable (MSR) will export the data from REDCap into an Excel file, prepare the data (incl. removal of any identifiers, and anything indicating the interpretation of grouping variable). A blinded data analyst (JBL) will conduct the primary analysis and subsequently the primary investigator (BE) will assist in the completion of secondary between-group analysis and interpretation of results. Data from all timepoints (baseline, 6 weeks, 3 months, and 6 months) will be included in the analysis of continuous outcomes.

Conclusions will be based on results at the three-month end point. Results of the 6-month end point will be considered exploratory and confirmatory conclusions about superiority will not be based on these.

Timing of outcome assessments

Outcomes are measured at baseline, 6 weeks, 3 months, and 6 months-follow-up. Exempt is adverse events, which will be evaluated continuously during the intervention period and GICS which is measured at all follow-ups at 6 weeks, 3 months, and 6 months.

Section 4: Statistical principles

Confidence intervals and *P* values

All statistical tests will be reported with two-sided 95% Confidence Intervals and evaluated with a significance level of 5% (e.g., $p \leq 0.05$) (19).

Adherence and treatment protocol deviations

Adherence to the intervention will be defined as participation in both, of the two mandatory, sessions of pain science education with the PNE4Adults in the Intervention group. Participation, including the time spent on the education is registered by the physiotherapists delivering the PNE4Adults immediately after each session.

Since the "usual care" does not specify any elements that have to be included, there are no assessment of adherence to this part (applies to both groups).

Adherence will be reported as number and percentage of participants in the intervention group participating in both PNE4Adults-sessions.

The per-protocol analysis will solely include those that:

1) Receive the allocated intervention (Control / Intervention)
2) Adhere to intervention (according to above)
3) Complete follow-up at three months

Analysis population

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.

The per-protocol population is restricted to the participants who are compliant to the protocol as described above.

Section 5: Trial Population

Screening data

All patients with Musculoskeletal conditions referred to rehabilitation in Holbæk, Solrød and Køge municipalities are screened, but only those that are eligible to participate (as per in- and exclusion criteria) are noted. The time frame in which patients are screened for eligibility will be reported.

Eligibility

This trial will include patients referred to rehabilitation at a community-based rehabilitation center with chronic MSK pain. Patients will be recruited from community-based rehabilitation in Køge, Solrød, and Holbæk Municipalities.

The following selection criteria will be used:

Inclusion

- Patients referred for rehabilitation in the municipalities Køge, Holbæk, and Solrød
- With chronic (>3 months) musculoskeletal pain.
- Adult patients (≥18 years) – no upper limit (20)
- Able to understand, speak, and write Danish.

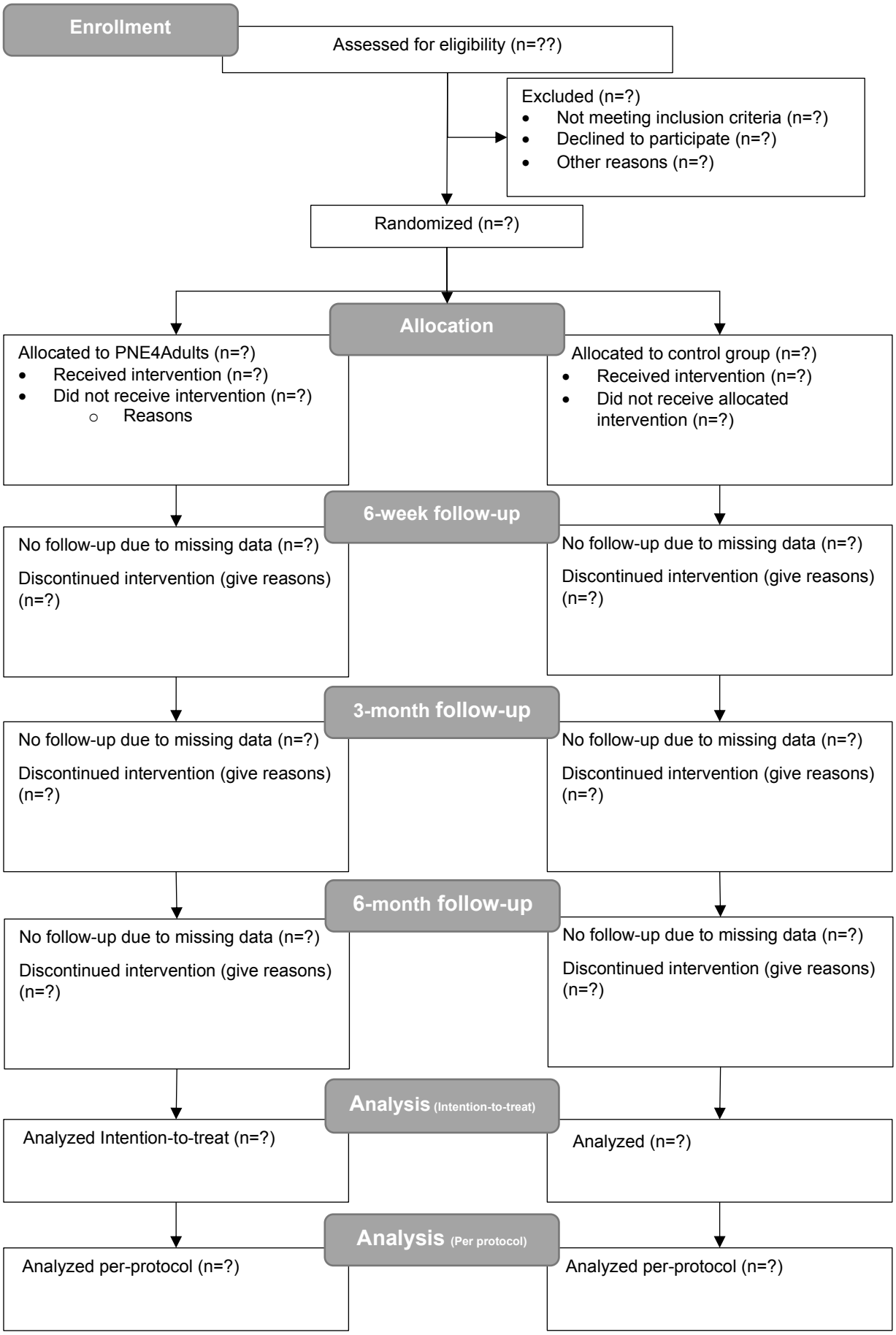
Exclusion

- Known cognitive deficits (e.g., dementia).
- Diagnosed with cancer or other serious pathologies, e.g., cauda equina.
- Pregnancy
- Drug addiction defined as the use of cannabis, opioids, or other drugs.
- Neurologic or psychiatric diagnoses that hinder participation, e.g., stroke and borderline.
- Lack of ability to cooperate.

Recruitment & Withdrawal/follow-up

Recruitment and follow-up will be reported in a flowchart, as illustrated in figure 1 below.

Figure 1: Flowchart of inclusion and follow-up



Baseline patient characteristics

Figure 2 below shows the flow of inclusion, randomization and when questionnaires are answered. At baseline (T1), socio-demographic data will be collected: age, sex, marital status, work status, and education level. Additionally, diagnoses and co-morbidities, pain duration, self-reported usage of pain medication, and sick-leave, Central Sensitization Inventory (CSI) (21) and Brief Health Literacy scale for Adults (B-HLA) (22) to characterize their clinical condition will be collected. Immediately following randomization, the patient is asked to answer the question: *"How confident are you that this treatment option will be successful in improving your MSK pain"* with response options being: *'Very confident', 'Confident', 'Neither or', 'Unsure'*, or *'Very unsure'*. We will consider the patients as confident, if they choose the options *"Very confident"* and "*Confident"* and not confident if they choose the options *"neither or", Unsure" or "Very unsure".*

Figure 2: Flow of inclusion, randomization and timepoints for follow-up

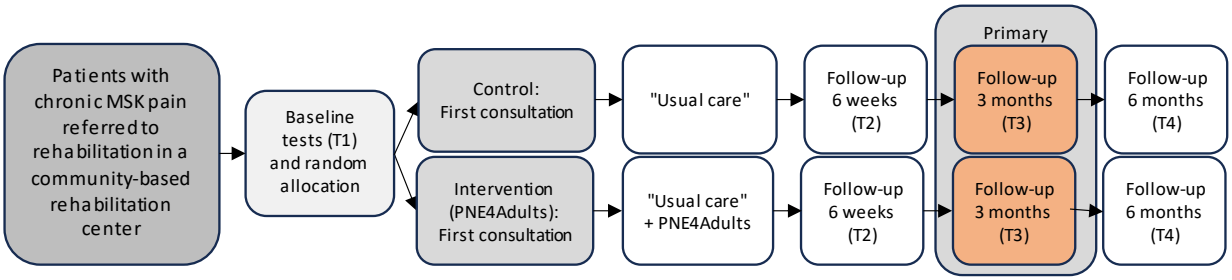


Figure 3 illustrates when which data are collected, as described below.

Figure 3. Summary of measures to be collected (SPIRIT figure)

	STUDY PERIOD					
	Pre-allocation		**Allocation**	**Post-allocation**		
	Enrollment	Baseline T1		6 weeks T2	**3** months T3	6 months T4
Enrolment:						
Eligibility screening	✓		✓			
Informed consent	✓	✓				
Allocation			✓			
Confidence in allocation			✓			
Intervention:						
Intervention (PNE4Adults + "Usual care")			✓	✓	✓	✓
Control ("Usual care")						
Baseline assessments:						
Baseline demographics		✓				
Brief Health Literacy Adult (B-HLA)		✓				
Central Sensitization Inventory (CSI)		✓				
Outcome questionnaires:						
Musculoskeletal Health Questionnaire (MSK-HQ)		✓		✓	✓	✓
Mean Pain (NRS)		✓		✓	✓	✓
Pain Interference (BPI)		✓		✓	✓	✓
Concept Of Pain Inventory (COPI-Adult)		✓		✓	✓	✓
Pain Catastrophizing Scale (PCS)		✓		✓	✓	✓
Pain Self-Efficacy (PSEQ)		✓		✓	✓	✓
Tampa Scale of Kinesiophobia (TSK-11)		✓		✓	✓	✓
Patient Specific Functional Scale (PSFS)		✓		✓	✓	✓
Physical activity level		✓		✓	✓	✓
Other:						
Adherence			◆—	—	—	—◆
Time spent on treatment			◆—	—	—	—◆
Adverse events			◆—	—	—	—◆

Before randomization (T1) the following questionnaires are answered the first time, and repeated again at T2, T3 and T4: Musculoskeletal Health Questionnaire (MSK-HQ) + one question on physical activity level (18), Mean pain intensity (average of two numeric rating scales – most severe pain intensity during past 24 hours, and average pain intensity during past 24 hours, on a 0-10 numeric rating scale) (23), Pain interference (Interference part of the Brief Pain Inventory (BPI)) (24,25), Pain knowledge (Concept of Pain Inventory – adult (COPI-Adult (DK))) (26,27), Pain catastrophizing (Pain Catastrophizing Scale (PCS)) (28), Pain self-efficacy (Pain Self-Efficacy Questionnaire (PSEQ)) (29), Fear of movement (Tampa Scale of Kinesiophobia (TSK-11)) (30), Patient specific functional limitations (Patient-Specific Functional Scale, 0-10 scale) (31,32)). Throughout the trial, any adverse events will be noted by the physiotherapist, based on self-report from patients.

Continuous data will be presented as mean and SD if data has a normal distribution and as median and range if data has a non-normal distribution. 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 (33). Instead, the clinical importance of any imbalances will be considered.

Section 6: Analysis

Outcome definitions. List and describe each primary and secondary outcome including details of:

Primary outcome will be change in Musculoskeletal Health from baseline measured with the Musculoskeletal Health Questionnaire (MSK-HQ) (18) to three months (T3). Secondary endpoints will be at 6 weeks (T2) and 6 months (T4). MSK-HQ is a patient reported outcome measure (PROM) with 14 items, ranging from 0 (worst possible score) to 56 (best possible score) with high reliability (ICC 0.86 (CI95% 0.81 – 0.91)), that measures different aspects of musculoskeletal health. The minimum important difference is 8.6 points on the Danish version (18). It is a continuous score.

Secondary outcomes – continuous will be changes in below mentioned outcome measures from baseline to six week, three months and six months follow-up measured with the in brackets mentioned PROM.

- Mean pain intensity (average of two numeric rating scales – most severe during past 24 hours, and average during past 24 hours, on a 0-10 numeric rating scale) (23),
- Pain interference (Interference part of the Brief Pain Inventory (BPI)) (24,25),
- Concept of pain (Concept of Pain Inventory – adult (COPI-Adult (DK))) (26,27),
- Pain catastrophizing (Pain Catastrophizing Scale (PCS)) (28),
- Pain self-efficacy (Pain Self-Efficacy Questionnaire (PSEQ)) (29,34),
- Fear of movement (Tampa Scale of Kinesiophobia (TSK-11)) (30,35),
- Patient specific functional limitations (Patient-Specific Functional Scale, 0-10 scale) (31,32)).

Secondary outcomes - dichotomous

- Patients' impression of change (Global Impression of Change scale (GICS) (36) as a single-item rating by participants using a 7-point rating scale with the options *"very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse,"* and *"very much worse"*), (Dworkin et al., 2005) We will consider the responses as improved, if they choose the options *"very much improved," "much improved," (options 7 and 6) and not improved if they choose the options "minimally improved," "no change," "minimally worse," "much worse,"* and *"very much worse"* (options 1-5) (37)
- Patient satisfaction with current symptom state (Patient Acceptable Symptom State (PASS)) with the wording: *"Taking into account your level of pain and also your functional impairment, if you were to remain for the next few months as you are today, would you consider that your current state is satisfactory?"* (38),

Secondary outcomes - other

- The time spent on consultations will be measured in hours and divided into individual consultation and group-based consultation.
- Physical activity levels in the past week (One question on the MSK-HQ) (18).

Analysis methods

We will use Q-Q plots and histograms to assess data normality and analyses are performed following the intention-to-treat principle such that randomized participants will be analyzed according to the treatment group to which they were originally assigned, regardless of treatment received, crossover or non-adherence.

Between-groups comparisons

For the primary outcome (MSK-HQ) **and all secondary continuous outcomes, we investigate the** between-group difference in change from baseline to three months (T3) as the primary endpoint.

Analyses will include outcome data for baseline and all available follow-up time-points. The blinding will be ensured, by having one unblinded researcher extract data from REDCap, removing all group identifiers (e.g., time spend on intervention), and removing the identifier of Group 1 and Group 2. Then there is no way for the blinded data analysist to identify the different groups, and the blinded researcher will continue the data management.

We will visually explore the anonymized trajectories (Group 1 and Group 2) of improvements before applying the statistical model to the data. This will ensure that our choice of model matches the specific trajectories. This will be done by a researcher blinded to group allocation.

We expect to use a linear mixed effects model with the participant as random effect. The baseline MSK-HQ value, time (6 weeks, 3 and 6 months as categorial variable), group allocation (group 1/group 2) and term for interaction between time and group will be treated as fixed-effect variables. Covariance structure will be determined based on the Akaike Information Criterion (AIC)/MAICE procedure (39).

Conclusions about intervention superiority will be based on the between-group differences or the lack hereof in the change from baseline of the primary outcome and the primary endpoint (three months).

Dichotomized secondary outcomes will be analyzed using the Chi squared test to compare proportions, and odds ratio estimates with corresponding 95% CI will be reported. As recommended in CONSORT (33), Relative Risk will be reported, to help interpretation (40).

Descriptive analysis will be made to map the time spent on delivering the PNE4Adults part 1, part 2 and on which parts of Part 3 (if any) were delivered. Time spent on consultations, physical activity levels and any adverse events will also be descriptively reported.

All analyses of secondary outcomes will be considered explorative and not adjusted for multiple testing.

Multiple analysis

We have chosen not to adjust for multiple comparisons in this study. Our primary conclusions will be based solely on the results of the primary analysis, which examines the between-group difference in change in MSK-HQ at the three-month follow-up. Secondary analyses and moderation analyses are considered exploratory and are intended to generate hypotheses rather than provide definitive conclusions.

This approach aligns with recommendations to focus on the primary outcome to minimize the risk of misinterpretation due to multiple testing (41). While we acknowledge that secondary analyses may yield false-positive results due to the lack of adjustment, we consider this acceptable in this context as these analyses are exploratory and will be reported as such in our results. To ensure transparency, we will report all results with complete p-values and confidence intervals, and the interpretation of findings will be cautious, clearly distinguishing between primary and secondary results.

This approach ensures that the study design and analyses remain focused on the main research question while also leveraging the collected data to explore potentially relevant associations.

Missing data

Missing data will be assumed Missing at Random using the maximum likelihood estimation inherent in LMM.

Since the linear mixed effects model includes all patients with at least baseline MSK-HQ score as a repeated observation of the dependent variable, it enables us to include the patients missing all follow-up data. There will be no imputations (42). Number of data points will be displayed in publication.

Additional analyses

Sensitivity analysis:

The following sensitivity analysis will be performed on the primary outcome and reported alongside the primary analysis in the primary report:

- A per-protocol sensitivity analysis using the same method as with the main analysis.
- A sensitivity analysis, where we use selective imputations as suggested by Twisk et al. (42).

Subgroup analysis:

We will run explorative moderator analyses, as predefined in table 3, to assess the potential effect modifiers of treatment effect for Intervention ('PNE4Adults' integrated into "usual care") compared to "usual care alone".

Table 3: Potential moderators, hypothesized direction, and rationale for effect

Moderator	Hypothesized effect direction	Rationale	Data structure / Level as collected	Data format for analysis	Outcome at three months
Health literacy	Greater effect in those with high levels of health literacy	Low health literacy is a known to determine poorer outcomes. We hypothesize that better health literacy means that patients understand the teachings better and have more improvement in outcomes.	Continuous. Brief Health Literacy Scale Adults (B-HLA) 10 questions with 1-4 response options, sum score 10-40, higher scores reflecting better health literacy	Continuous	MSK-HQ COPI-Adults PSEQ
Pain self-efficacy	Greater effect in those with low levels of pain self-efficacy	As the intervention (PNE4Adults) is thought to target, amongst others, pain self-efficacy, our hypothesis is that a potential effect of the intervention will be more pronounced in patients with lower pain self-efficacy at baseline.	Continuous. Pain Self-efficacy Questionnaire (PSEQ). 10 questions with response options 0-6, Sum score 0-60, higher score indicates greater self-efficacy when faced with pain.	Continuous	MSK-HQ
Sensitization	Greater effect in those with many symptoms of	Explaining pain, incl. central and peripheral sensitization and incorporating this	Continuous. Central Sensitization Inventory (CSI)	Continuous	MSK-HQ

	central sensitization	knowledge into rehabilitation is a target of the PNE4Adults. We therefore propose that those with more symptoms of sensitization will benefit more.	25 questions with response options 0-4, sum score 0-100, higher scores indicate more signs of sensitization.		
Pain Knowledge	Greater effect in those with low levels of pain knowledge	One target of the PNE4Adults is explaining what pain is, and possible factors influencing the pain experience. The less you know beforehand, the greater the possibility of improvement. Vise versa, if you already have the knowledge, there is no added effect of being taught about it.	Continuous. Concept of Pain Inventory (COPI-Adult). 13 questions with response options 0-4, sum scores 0-56, higher scores indicate more updated contemporary pain knowledge	Continuous	MSK-HQ

Each potential moderator will be analyzed separately.

The moderator analyses apply the same statistical approach as the main analysis and includes participant as random effect. Included as fixed effects are baseline score for outcome variable (MSK-HQ), baseline score for moderator variable (grand mean centered), all time-point (categorial variable), group allocation and the interaction between baseline moderator variable, time, and group allocation. All follow-up measurements of the outcome variable are included as repeated measurements.

The analysis will be conducted with continuous moderator variables and evaluated statistically.

Interaction plots are used to visualize the difference in effect at different levels of the moderator to help interpretation in the clinic. For this purpose, we will apply cut-offs for individual moderator variables based on the distribution of date (e.g. mean and ±SD) but also for suggested cut-off score when available from the literature. Specifically, for the CSI >40 is considered a sign of central sensitization (43); for B-HLA the authors of the scale suggest using cut-off scores for the converted scale (The Health Literacy for School Aged Children, HLSAC), e.g., low score (10-25), moderate (26-35) and high score (36-40) (22); for PSEQ >22 is considered as high (44). There are no suggested cut-off scores published on the COPI-Adult. Depending on the distribution of responses in each proposed category, we might choose to collapse categories or do sensitivity analysis to test the effect of different cut-points.

Further exploratory analysis may be conducted if deemed relevant, specifically mediation analysis if the data suggests a possible mediating effect, to explore mechanisms of the intervention and potentials for improving the intervention.

Patient- and Public Involvement (PPI):

In the iterative development of the intervention, stakeholders (both patient representatives and physiotherapists) were involved, and the feasibility of the intervention was tested in a municipality setting on twenty consecutively referred patients with chronic MSK-pain (Eiger, B., Rathleff, MS. et al. 2024 – under review). When choosing secondary aims, the wishes of clinical physiotherapists were combined with relevant areas from the literature to ensure relevance from an academic as well as clinical perspective. We plan to involve relevant stakeholder in the interpretation and dissemination of results as suggested by Goulão et al., (45).

Harms

Safety and adverse events:

Adverse events are not expected, as the intervention is educational (46). However, information will be gathered on any adverse events in agreement with the IMMPACT recommendations (36,47). Adverse events will be collected throughout the trial, and any adverse events will be reported as numbers and %. Patients will be asked to report any adverse events to their physiotherapist as soon as they occur. Muscle soreness or mild increase in pain is considered normal when initiating physical rehabilitation and is not considered an adverse event. There will be a Safety Monitoring Committee (SMC).

Safety Monitoring Committee:

Ensuring the safety of all participants in this study is important. With the single purpose of handling any adverse events a Safety Monitoring Committee (SMC) will be set up. The SMC will consist of the principal investigator (BE), main supervisor (MBC) and a medical doctor, Jens Lykkegaard Olesen, who is not otherwise involved in the study. In case of an adverse event, there will be an online meeting at which the event will be assessed and possibly graded (according to the Common Terminology Criteria for Adverse Events v4.03 (48)), the relation to the study determined, assisting the clinician in determining course of action, and deciding whether the participant can continue or should be withdrawn from the study. Action and treatment of adverse events will start immediately following the usual treatment protocols. Once annually a list of any adverse events will be reported to the Ethical Committee.

Statistical software

Data is collected and stored in REDCap (Vanderbilt University, Nashville, TN, USA), which is hosted at a secure server at Aalborg University. In accordance with GDPR-rules, the data management plan has been approved by Aalborg University “Grants and Contract Unit” (j.nr. 2024-068-04552) before commencing the study. Data will be exported to Microsoft Excel (Microsoft Corporation, Washington, USA) where it they will be prepared for analyses. Analysis will be performed in an up-to-date statistical software, specified in the publication.

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