Digital sleep therapy in patients with Musculoskeletal complaints and insomnia

Statistical Analysis Plan

Version 1.0

Administrative information

Sponsor name	N/A
Sponsor address	N/A
EudraCT number / REC no	Ethical application reference 496297 (REK-Midt)
Trial title	Digital sleep therapy in patients with musculoskeletal complaints and insomnia
Trial ID	
Trial registration number	ClinicalTrials.gov identifier: NCT05572697

SAP and protocol version

SAP version and date	Version 1.0, 07.11.2024
Protocol version	App-Delivered Cognitive-Behavioral Therapy for Insomnia Among Patients | NSS (dovepress.com)

SAP revision history

Protocol version	SAP version	Date changed	Description and reason for change

Roles and responsibilities

The project management team responsible for the overall implementation of the project consists of Lene Aasdahl, Eivind Schjelderup Skarpsno, Melanie Rae Simpson, and Nora Boldermo Rian. All employed at the department of Public Health and Nursing at the Norwegian University of Science and Technology. Aasdahl is the project leader leading the project together with Skarpsno. Simpson is the trial statistician. Rian wrote the first draft of the SAP, which was edited in collaboration with all the authors. All authors approved the final version.

Signatures of:

Principal Investigator: Lene Aasdahl

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Abbreviations

SAP	Statistical Analysis Plan
CBT-I	Cognitive-behavioral therapy for insomnia
dCBT-I	Digital versions of CBT-I
RCT	Randomized clinical trial
ISI	Insomnia Severity Index
NPD	Norwegian Prescription Database
NAV	National Insurance Administration
HSCL-25	Hopkins Symptom Checklist, 25 questions
EQ-5D	European Quality of Life – 5 Dimensions
PSFS	Patient Specific Functional Scale
ITT	Intention to treat
SD	Standard deviation
IQR	Interquartile range
OR	Odds ratio
HUNT3 PA	Trøndelag Health Study (HUNT Study), physical activity questionnaire

Table of contents

1. Introduction

This Statistical Analysis Plan (SAP) should be read in conjunction with the published trial protocol: *App-Delivered Cognitive-Behavioral Therapy for Insomnia Among Patients with Comorbid Musculoskeletal Complaints and Insomnia Referred to 4-Week Inpatient Multimodal Rehabilitation: Protocol for a Randomized Clinical Trial* [1]**.** The information available here provides a more detailed description of the "Statistical analysis" section.

1.1 Purpose and scope of the statistical analysis plan

This document details the proposed analyses of the main paper reporting results from the study "*Digital sleep therapy in patients with musculoskeletal complaints and insomnia referred to inpatient multimodal pain rehabilitation"*. Any deviations from the analyses outlined in this SAP will be described and justified in the final report of the trial, including the inclusion of any analyses suggested by journal editors and referees. Modifications will be carefully considered and, as far as possible, follow the broad principles set out here.

First and foremost, this SAP describes the analysis of the primary and secondary outcomes. Subsequent exploratory analyses are also expected to follow the broad principles of this SAP but are not described in detail here.

The details presented here shall not prohibit accepted practices, such as data transformation prior to analysis. When possible, such data management and modelling decisions will be undertaken prior to revealing the treatment allocation. The final analysis strategy will be available on request when the papers are submitted.

1.2 Background and rationale

Insomnia is prevalent among patients receiving treatment for long-term musculoskeletal complaints in inpatient rehabilitation settings. Cognitive-behavioral therapy for insomnia (CBT-I) is effective for improving sleep quality in patients with pain, but a lack of therapists often limits the capacity to use this therapy in rehabilitation programs. To increase the availability of CBT-I, self-guided, fully automated digital versions of CBT-I (dCBT-I) have been developed. An advantage of dCBT-I is that it can be an add-on to usual care. The aim of this randomized clinical trial (RCT) is to evaluate the effectiveness of app-delivered dCBT-I adjunct to inpatient multimodal rehabilitation for individuals with comorbid musculoskeletal complaints and insomnia, compared with rehabilitation (usual care) only.

1.3 Objectives

1.3.1 Primary objective

The primary objective of this trial is to evaluate the effectiveness of dCBT-I on insomnia severity for patients with long-term musculoskeletal complaints in inpatient multidisciplinary rehabilitation compared to inpatient multidisciplinary rehabilitation only during 12 months of follow-up. The main assessment point will be 3 months after end of rehabilitation.

1.3.2 Secondary and exploratory objectives

Secondary objectives:

1) Examine the difference in the proportion of participants that achieves an 8-point improvement in their ISI-score between inpatient multidisciplinary rehabilitation + dCBT-I (intervention group) and inpatient multidisciplinary rehabilitation only (control group), 3-, 6-, and 12 months after end of rehabilitation.
2) Evaluate the effectiveness of the intervention on pain intensity, fatigue, health-related quality of life, physical function, and physical activity at 3-, 6-, and 12 months after end of rehabilitation.
3) Evaluate the long-term effectiveness of the intervention on sickness absence and use of prescribed sleep and pain medication during 12 months of follow-up after rehabilitation (this will be done if successful register linkage within the time frame of the project).

If the data material allows it, it will be relevant to examine the following exploratory objectives:

4) Explore whether changes in pain intensity and fatigue mediate the effect of dCBT-I on insomnia severity.
5) Explore whether sex, age, symptoms of anxiety and depression, pain intensity and level of physical activity at baseline moderate the effect of dCBT-I on insomnia severity and secondary outcomes (pain intensity, health-related quality of life, sickness absence and use of prescription sleep and pain medication).

2. Study design

2.1 Study design

The trial is as a cluster-randomized clinical trial with two parallel groups, investigating the effects of dCBT-I on insomnia symptoms for patients with comorbid musculoskeletal complaints and insomnia in inpatient rehabilitation compared with traditional inpatient rehabilitation only (figure 1). To maximize the number of participants receiving the additional treatment (dCBT-I), the participants are randomized to the intervention and usual care at a ratio of 2:1.

2.2 Randomization and treatment assignment

The randomization will be at group level to avoid contamination between members of the same rehabilitation group. Each group are randomized using a computer-generated block randomization provided by the Clinical Research Unit (Project support) at the Faculty of Medicine and Health Sciences at the Norwegian University of Science and Technology (third party).

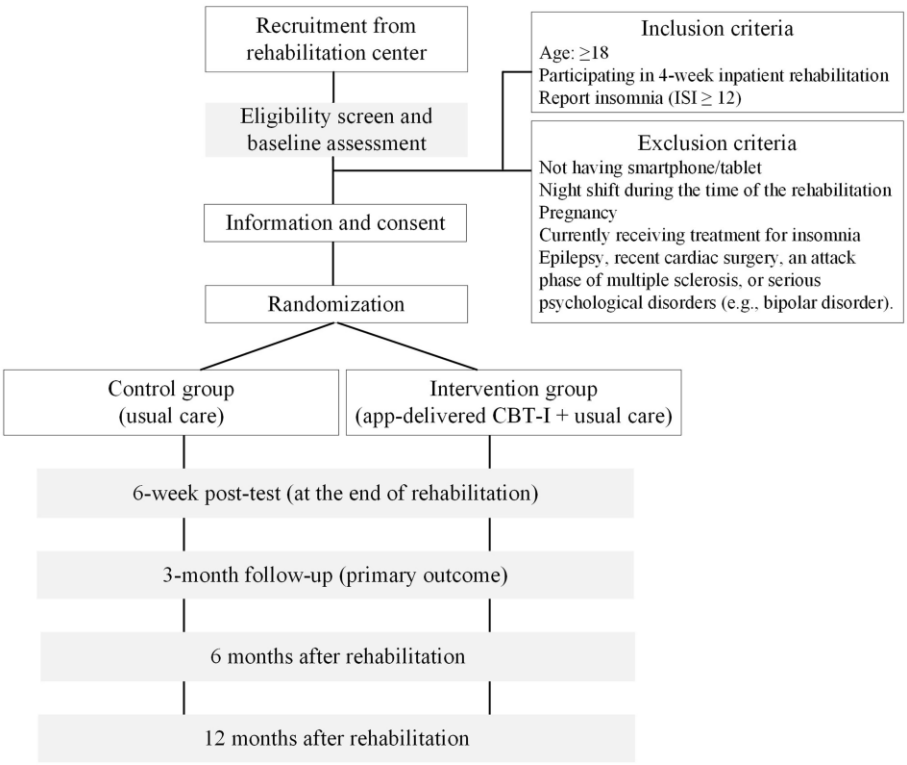

Figure 1 Flow of participants in the study

2.3 Determination of sample size

We anticipated that around five of 10 patients will have insomnia within each rehabilitation group and that the average Insomnia Severity Index (ISI)-score for participants completing usual treatment will be 15 (SD = 4). An average 4-point improvement on the ISI score is considered a meaningful change. In order to maximize the number of participants receiving the additional treatment (dCBT-I), we will randomize the participants to the intervention and usual care at a ratio of 2:1. Recruiting 15 clusters with 2:1 randomization will achieve 80% power to detect a 4-point difference between the intervention and usual treatment group, with a conservative assumption that the intraclass correlation is 0.2 and the coefficient of variation in cluster size up to 0.7, and with a significance level of 5%. This would mean that around 150 participants will be screened to give an expected sample size of 75 (50 in dCBT-I + usual care and 25 in usual care). We expect a dropout rate of approximately 20% and that around 50% of the participants in the intervention group will complete at least four of the dCBT-I modules. Given that the per-protocol analysis is of particular interest in this study, we aim to recruit 21 clusters to account for the fact that we expect an average of four participants per cluster in the control group to complete the follow-up, and an average of two participants in the intervention group to complete at least four of the modules and attend the follow-up.

2.4 Framework

The trial aims to test if dCBT-I is superior to usual care. Two-sided tests will be used for both primary and secondary objectives.

2.5 Statistical interim analyses and stopping guidance

Since the participants receive medical supervision during the 4-week rehabilitation, we do not plan any interim analyses.

2.6 Timing of final analysis

The main analyses will be performed at 12 months after end of rehabilitation. The primary outcome measure point is 3 months of follow-up. Results for 6- and 12 months of follow-up will be presented in the same publication.

2.7 Data sources and timing of endpoint assessments

2.7.1 Data sources

In the project we will use questionnaire and registry data. For the main outcome, questionnaire data will be used.

Questionnaires

Self-reported web-based questionnaires are answered at five time points: at baseline (prior to randomization), 6 weeks (at the end of rehabilitation), at 3 months (primary outcome measurement), 6 months, and 12 months after end of rehabilitation.

In addition, diagnoses and use of medication at baseline will be available through the electronic patient records.

Registry Data

Registry-based data will be obtained for 12 months of follow-up after rehabilitation from the Norwegian Prescription Database (NPD) and the National Insurance Administration (NAV). From NPD, we will obtain data on use of sleep and pain medications and assess the proportion of participants that obtain prescriptions of these medications during the follow-up. From NAV, we will obtain data on use of medical benefits (sick leave, work assessment allowance and disability pensions). Work participation outcomes will include both total number of days of sickness absence during 12 months follow-up and the probability of being at work (i.e., without medical benefits) each month during the same period.

2.7.2 Timing of endpoint assessments

Table 1. Schedule for assessments

	Study period				
	Enrolment	**Post-rehabilitation**			
TIMEPOINT	***Baseline***	***End of rehabilitation***	***3 months***	***6 months***	***12 months***
ASSESSMENTS:					
Age Sex Education Work status Work satisfaction Work ability Work expectations Sleep and pain medication (from journal)	X				
Anxiety and depression (HSCL-25)	X	X			
Primary outcome Insomnia severity index (ISI)	X	X	X	X	X
Secondary outcomes					
Pain intensity	X	X	X	X	X
Fatigue	X	X	X	X	X
Health-related quality of life (EQ-5D)	X	X	X	X	X
Physical function (PSFS)	X	X	X	X	X
Physical activity (HUNT3 PA)	X		X	X	X
Registry data Sickness absence and disability pension Sleep and pain medication	→				

HSCL-25: Hopkins Symptom Checklist, 25 questions. EQ-5D: European Quality of Life – 5 Dimensions. PSFS: Patient Specific Functional Scale. HUNT3 PA: Trøndelag Health Study (HUNT Study), physical activity questionnaire.

3. Statistical principles

3.1 Confidence intervals and p-values

We will use two-sided tests and report mean differences with 95% confidence intervals.

3.2 Adherence, protocol deviations and protocol violations

Adherence will be defined as completing at least the 4 first modules of dCBT-I as stimulus control is in module 4.

3.3 Analysis populations

3.3.1 Intention to Treat (or Full Analysis Set)

Effect analyses of primary and secondary outcomes will be performed after the intention-to-treat (ITT) principle, i.e., we will include all participants that were included and randomized.

3.3.2 Per-Protocol Analysis Set

Per-protocol analyses will be performed for individuals who complete ≥4 dCBT-I modules to explore whether patients who complete ≥4 dCBT-I modules have a greater effect on insomnia severity 3 months after intervention than patients who complete <4 dCBT-I modules.

3.4 Allocation concealment, blinding and order of analysis

3.4.1 Allocation concealment

As the groups are randomised using a computer-generated block randomisation provided by a third party (the Clinical Research Unit at the Faculty of Medicine and Health Sciences at the Norwegian University of Science and Technology), the research team will not be able to influence the randomization process in any way and the allocation sequence is hence concealed until the moment of assignment.

3.4.2 Blinded statistician

As we randomize 2:1 blinding is a challenge. Therefore, we will write and publish the syntax for the main analyses before the analyses are performed. The researcher performing the analyses will present the results graphically without group labels, group size, and confident intervals to the rest of the project group. A written interpretation of the results will then be conducted by the project group before the group information is revealed.

4. Presentation of study population

4.1 Screening data, eligibility and recruitment

See section 2.1 for flowchart over participants in the study (figure 1).

4.2 Withdrawal / follow-up

We will describe how many participants drop out during the study and reason for this if available (due to ethical consent there is no obligation for provide a reason for dropping out). If participants do not answer the questionnaire, they will be registered as 'lost to follow-up'. If participants withdraw their consent, they will be excluded unless their data has already been included in analyses or published.

4.3 Baseline patient characteristics

Descriptive statistics will be presented stratified by group allocation. Descriptive statistics will include age, gender, education, work status, medical benefits, pain intensity, anxiety and depression, sleep and pain medication, fatigue, health-related quality of life, physical activity, physical function, and insomnia severity. Categorical and binary variables will be presented as counts and percentages, continuous variables will be presented as means and standard deviation (SD) or medians and interquartile range (IQR), as appropriate.

5. Analysis

5.1 Outcome definitions

5.1.1 Primary outcome

The primary outcome is insomnia measured by ISI at three months follow-up. ISI is the gold standard self-report measure of insomnia severity in clinical practice, consisting of seven items assessing symptoms of insomnia such as difficulty falling or staying asleep, satisfaction with sleep, and degree of impairment with daytime functioning. The total score of ISI ranges from 0 to 28. ISI has been validated and has proven sensitive to therapeutic changes [2]. For the primary analyses ISI will be included as a continuous variable. Se table in 2.7.2 for details concerning measurement time.

5.1.2 Secondary outcomes

1) Difference in the proportion of participants that achieves an 8-point improvement on ISI between the intervention group and the control group. This is in accordance with the literature suggesting an improvement of the ISI score ≥8 points is a meaningful improvement, indicating that the intervention has a positive impact on the individual's sleep [2].
2) The effect of the intervention on
    a. pain intensity measured using a visual analogue scale from 0 to 100.
    b. fatigue measured using a visual analogue scale from 0 to 100.
    c. health-related quality of life measured by EQ-5D.
    d. physical function measured by PSFS.
    e. physical activity measured by three questions about frequency, duration and intensity of physical activity per week

The above listed outcomes will be analyzed for 3-, 6-, and 12 months of follow-up, with 3 months being the main assessment point.

In additional publications, we will investigate the long-term effects (12 months) of dCBT-I on sickness absence and use of prescribed sleep and pain medication.

1) Work outcomes: 1) Difference between the two groups in total number of sickness absence during 12 months of follow-up and 2) probability of working (i.e., not receiving medical benefits) each month during 12 months of follow-up. Based on registry data from NAV.
2) Difference in the proportion of participants that obtain prescriptions for sleep and pain medication between two groups during 12 months of follow-up. Based on registry data from NPD.

5.2 Analysis of primary outcome

We will use linear mixed model analysis to estimate mean difference in ISI between the two groups at 3, 6 and 12 months of follow-up, with the primary outcome measurement at 3 months. The model will include participant ID as a random effect and time, time–group interaction and baseline covariates as fixed effects. Of baseline covariates we will include age, sex, and education. Determination of possible categorizing of the covariates will be done before unblinding and published in an updated version of this SAP.

The assumption of normally distributed residuals will be assessed by visual inspection of histograms and Normal Q-Q plots. Model assumptions for mixed models will be checked: residuals (approximately) normally distributed and homogeneity of residual variance (homoscedasticity).

5.2.1 Sensitivity analyses

We do not anticipate strong cluster-level effects; however, we will conduct a sensitivity analysis including rehabilitation group in the mixed linear model with follow-up timepoints as level 1, participants as level 2, and rehabilitation group as level 3.

5.2.2 Subgroup analyses and treatment effect heterogeneity

If the data material allows it, we will explore whether age, anxiety and/or depression, pain intensity, level of physical activity, and specific combinations of insomnia symptoms at baseline moderate the effect of dCBT-I on primary outcomes. Each of these demographics and characteristics will be categorized into 2 or 3 categories based on examination of the dataset without randomization allocation information.

Decision whether the data material allows what is mentioned above will be conducted before the group information is revealed.

5.2.3 Missing data

We will use the linear mixed model analyses, which provides unbiased effect estimates under the assumption that the outcome data is missing at random.

5.3 Analysis of secondary outcomes

For binary secondary outcomes (e.g., clinically relevant change in ISI, minimal important change in PSFS), we will use a generalized estimated equation logistic model to estimate the odds ratio (OR) for achieving at least an 8-point improvement in ISI score. In these analyses, we will assume an exchangeable correlation structure and a robust variance estimator. For the other secondary outcomes, a mixed linear regression model will be used.

5.4 Pre-planned exploratory analyses

We plan to conduct exploratory analyses identifying whether changes in pain intensity and fatigue mediate the effect of dCBT- I on insomnia severity. Likewise, we will identify whether changes in insomnia symptoms and fatigue mediate the effect on pain severity. We will follow the international, consensus-based guidance for the reporting of mediation analyses of randomized trials. If the data material allows the analyses above to be conducted, the results will be published in an additional publication.

5.5 Statistical software

All analyses will be done using StataMP 18 (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC).

6. References

1. Skarpsno, E.S., *App-Delivered Cognitive-Behavioral Therapy for Insomnia Among Patients with Comorbid Musculoskeletal Complaints and Insomnia Referred to 4-Week Inpatient Multimodal Rehabilitation: Protocol for a Randomized Clinical Trial.* Nature and Science of Sleep, 2023(15): p. 799-809.
2. Morin, C.M., et al., *The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response.* Sleep, 2011. **34**(5): p. 601-8.