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Trials

STUDY PROTOCOL

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Digitally delivered cognitive behavioral therapy for insomnia (CBT-I) for patients with chronic pain and insomnia (The Back2Sleep Trial): study protocol for a randomized controlled trial

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Abstract

Background More than half of individuals with chronic pain also experience insomnia. Cognitive behavioral therapy for insomnia (CBT-I) is an effective and safe first-line treatment; however, access remains a major barrier to widespread implementation. This study aims to evaluate the effectiveness of a 9-week app-delivered CBT-I intervention, compared to an app-delivered sleep hygiene education program (active control), in reducing insomnia and pain severity in patients with disabling chronic pain and comorbid insomnia.

Methods The trial is a 1:1 randomized, single-blind, superiority trial randomizing 160 patients with disabling chronic pain and comorbid insomnia to either app-delivered CBT-I for 9 weeks or app-delivered sleep hygiene education for 9 weeks. Primary outcomes are the between-group differences in change in Insomnia Severity Index (ISI) and average pain intensity assessed using a 0–10 numeric rating scale (NRS) from baseline to post-interventions. Short-term secondary outcomes post-intervention include perceived effects on sleep and pain (Global Perceived Effect scales), sleep quality, thoughts and beliefs about sleep and pain, physical and mental health, and EQ5D-5L. Medium-term and long-term secondary outcomes (ISI, pain intensity, EQ5D-5L, health care costs, and use of sleep and pain medication) will be collected after 24 and 52 weeks. Exploratory physiological sleep metrics from at-home ear-electroencephalography (EEG) will be collected for five nights at baseline and for five nights during week 8.

Discussion This planned study addresses a critical need for identifying effective, safe, and easily accessible alternatives to the current treatments for patients with chronic pain and insomnia.

Trial registration ClinicalTrials.gov NCT06361914. Registered on April 17, 2024.

Keywords Chronic pain, Insomnia, Sleep, Cognitive behavioral therapy, CBT-I, Ear-EEG

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Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Digitally delivered cognitive behavioral therapy for insomnia (CBT-I) for patients with chronic pain and insomnia (The Back2Sleep Trial): study protocol for a randomized controlled trial
Trial registration {2a and 2b}	ClinicalTrials.gov ID: NCT06361914 (registered on April 17, 2024)
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Role of sponsor {5c}	The study is investigator-initiated. The study is sponsored and supervised by professor Henrik Bjarke Vaegter. The funders do not have any part in the design, conduct, or dissemination of the trial.

Introduction

Background and rationale {6a}

Chronic pain constitutes an increasing health and social burden [1]. More than half of patients with chronic pain report insomnia [2], and patients with comorbid insomnia often report more intense and widespread pain, compared to those who report being "good sleepers" [3]. One night with disturbed sleep has been found to reduce pain thresholds and impair the pain-inhibitory function in healthy individuals [4], and several population-based studies have demonstrated negative effects of insomnia on pain and found links between sleep disturbance and chronic musculoskeletal pain up to several years later [5]. Furthermore, studies have demonstrated improved sleep quality to be associated with reduced pain 1 year later [6] and positive correlations between improved sleep and improvement in pain after interdisciplinary pain treatment [7]. However, sleep disturbances are often considered to be primarily a consequence of chronic pain, leading insomnia to be overlooked or ineffectively managed with hypnotics or sleep hygiene advice. Therefore, efficacious, safe, and easily accessible alternatives to the current treatments for insomnia with potentially positive effects on pain for patients with chronic pain and insomnia are needed.

Cognitive behavioral therapy for insomnia (CBT-I) is an effective and safe treatment for insomnia [8, 9] and is recommended as first-line treatment by the European Sleep Research Society [10], and the American Academy of sleep Medicine [11, 12]. CBT-I is a combination of two or more commonly used cognitive-behavioral strategies, i.e., sleep restriction therapy, stimulus-control therapy, relaxation/deactivation, cognitive therapy, and sleep hygiene education. A number of randomized controlled trials of CBT-I have demonstrated beneficial effects not only on sleep efficiency and sleep quality but also on pain immediately after the intervention [13, 14], followed by even larger effects at 3–12-month follow-ups [15, 16].

While a full understanding of the involved mechanisms underlying this dual benefit is still lacking, they are likely multifactorial, involving neurophysiological, behavioral, and psychological pathways connecting sleep and pain processing systems [17, 18]. Poor sleep is likely to increase insomnia-induced hyperalgesia by modulating nociceptive processing, and the sleep restriction component of CBT-I may reverse this by stabilizing

sleep patterns [19]. Furthermore, the cognitive component of CBT-I targets dysfunctional beliefs about sleep, thereby reducing catastrophizing and negative affect [20], which are two well-known pain amplifiers. In addition, improved sleep has generally been shown to reduce levels of pro-inflammatory cytokines [21], improve mood, and reduce stress [22], which are all known factors that influence pain.

Despite being efficacious on sleep and pain with moderate to large effect sizes [14], the challenge remains to deliver CBT-I to all those in need, with the main barriers of face-to-face delivered CBT-I being insufficient number of trained therapists, costs associated with in-person delivered CBT-I, and physical and geographical constraints. Digitally or app-delivered CBT-I may overcome these constraints by offering a therapist-independent, individualized, scalable alternative that can be delivered at home both before, simultaneously, or after other pain treatments. While a meta-analysis of 11 trials has shown digital CBT-I to be effective in treating insomnia [23], the pain-relieving effect of digitally delivered CBT-I has only been explored in a small randomized controlled study in patients with chronic disabling pain and comorbid insomnia [24].

Objectives {7}

The aim of this randomized controlled clinical superiority trial is to evaluate the short-term, medium-term, and long-term effectiveness of a 9-week smartphone app-delivered CBT-I intervention, compared to a smartphone app-delivered sleep hygiene education program (active control), in reducing insomnia and pain severity in 160 patients with disabling chronic pain and comorbid insomnia.

One secondary aim is to examine whether app-delivered CBT-I is associated with reduced health care costs and reduced use of sleep and pain medication, and another secondary aim is to explore whether the treatment effect is mediated through changes in physiological sleep metrics assessed by a novel at-home ear-electroencephalography (ear-EEG) device in a subgroup of participants.

Trial design {8}

This study is a single-center randomized controlled single-blind parallel-group clinical superiority trial. Randomization comprises a parallel randomized (1:1) allocation of 160 patients aged ≥ 18 years with chronic disabling pain and insomnia treated with either app-delivered CBT-I or app-delivered sleep hygiene for 9 weeks.

Methods: participants, interventions and outcomes

Study setting {9}

This study is conducted at the Pain Center (Smertecenter Syd), the Department of Anesthesiology and Intensive Care, Odense University Hospital, Heden 7–9, 5000, Odense, Denmark. The setting is a specialized tertiary care University Hospital pain center.

Participants are recruited through advertisements, social media campaigns, and from the pain center waiting list. Participants expressing interest in the study are contacted by phone for an initial screening in relation to the eligibility criteria. Following the telephone screening, written information material is sent to potential eligible participants, and they are invited to a consultation at the Pain Center where the study information is repeated orally and the final inclusion and exclusion criteria are assessed.

Eligibility criteria {10}

Inclusion criteria

Danish speaking/understanding adults aged ≥ 18 years with chronic pain (pain duration ≥ 3 months). Pain must be present on "most days" or "every day" for the past 3 months, pain must limit the daily life or work activities on "some days," "most days," or "every day" during the past 3 months, the average pain intensity over the past 7 days must be ≥ 4 on 0–10 numeric rating scale (NRS) using the Graded Chronic Pain Scale Revised (GCPS-R) questionnaire [25], and insomnia symptoms must be ≥ 10 on the 0–28 Insomnia Severity Index (ISI) [26]. Participants must have access to a smartphone.

Exclusion criteria

The exclusion criteria are individuals (a) with known abuse of alcohol or other substances or who use benzodiazepines or other hypnotics, (b) with sleep disorders (e.g., sleep apnea, narcolepsy) or severe psychiatric disorders, suicide and self-injurious thoughts, and/or psychotic symptoms, (c) who have night shift work during the time of the trial, (d) who are pregnant, and (e) who do not have e-Boks (the official secure channel used to send official documents to Danish citizens and which is obligatory to be used in clinical trials for communicating with patients).

For the ear-EEG subgroup, participants ≥ 65 years will be excluded together with individuals where the anatomy of the outer ear makes it impossible to make ear-EEG earpieces, who have had a previous stroke or cerebral hemorrhage and any other structural cerebral disease, who suffer from severe teeth

grinding (bruxism), and who have allergic contact dermatitis caused by metals or are generally prone to skin irritation.

Who will take informed consent? {26a}

The primary investigator MLSO will be responsible for the informed consent procedure. Informed consent is obtained and signed by the participant and co-signed by the investigator at the first visit before data collection and before ear molding. Participants are informed that participation is voluntary, and that they can withdraw consent at any time without affecting their current or future treatment.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The study will be conducted in accordance with the Declaration of Helsinki and is approved by the Danish National Center for Ethics (VMK 2314393). Data processing in connection with the study has been reported to the region of Southern Denmark's list of on-going research projects via the Executive Secretariat at Odense University Hospital (24/11192) and Aarhus University's record of research projects (for ear-EEG data). Only study-relevant information will be collected. Data will be handled in accordance with the General Data Protection Regulation (GDPR) and the Data Protection Act "Act on the Processing of Personal Data" (Act No. 429 of 31/05/2000) and the "Law on the Status of Patients" (Act No. 482 of 01/07/1998). This trial does not collect biological specimens.

Interventions

Explanation for the choice of comparators {6b}

Sleep hygiene education is the commonly delivered non-pharmacological treatment for insomnia in patients with chronic pain.

Intervention description {11a}

After randomization, participants get access to the smartphone application Hvil®. This platform is used for both treatment arms (app-delivered CBT-I for 9 weeks or app-delivered sleep hygiene education for 9 weeks) to ensure that only the content is different, but the form of delivery is the same.

App-delivered CBT-I: The app-delivered CBT-I intervention in Hvil® (Fig. 1) is designed to be completed over a period of 9 weeks (5 weeks with the components described below and 4 weeks with maintenance of new habits) and is based on the current consensus concerning non-pharmacological treatment of insomnia [27] including the following treatment components:

➢ Sleep restriction is used to consolidate sleep and reduce fragmentation. During the initial week of intervention, participants limit their time in bed to match their average total sleep time as recorded during the baseline self-monitoring phase. Sleep efficiency will be continuously assessed using daily sleep diaries via the Hvil® application. Each subsequent week, the sleep window will be adjusted based on sleep efficiency metrics: if sleep efficiency reaches or exceeds 85%, the time in bed will be increased by 15

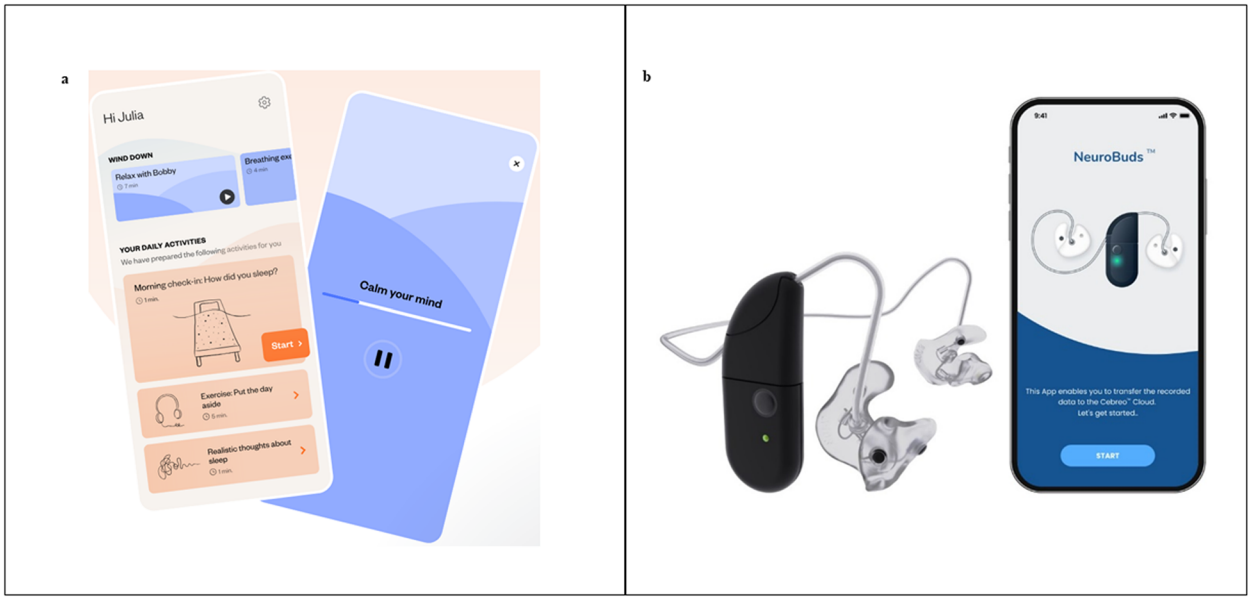

Fig. 1 **a** Hvil® application interface; **b** ear-EEG device for evaluation of physiological sleep outcomes

min; if sleep efficiency falls below 85%, the sleep window will be reduced by 15 min. This titration process will be repeated weekly to promote a stable sleep pattern and maintain an efficiency threshold of 85% [28, 29].

➢ Stimulus control therapy entails behavioral instructions to strengthen the association between bed and sleep and to eliminate conditioning of non-sleep behavior and bed. Instructions include going to bed only when sleepy and avoiding non-sleep behavior in the bedroom. If the person lies in bed for 15–20 min unable to sleep, they are instructed to leave the bedroom and only return when sleepy [28, 30].

➢ Cognitive therapy helps to identify, challenge, and modify dysfunctional beliefs about sleep. Such misconceptions may include an excessive focus on the potentially catastrophic consequences of sleep loss, unrealistic expectations of the amount of sleep needed, or faulty attributions about the causes of insomnia [31]. These misconceptions are modified and replaced by realistic alternatives using cognitive restructuring techniques [32].

➢ Deactivation/relaxation training involves methods to reduce somatic tension and limit intrusive thought processes that interfere with sleep. Specific relaxation techniques include progressive muscle relaxation (i.e., active tensing of muscle groups and then consciously relaxing them), guided imagery (i.e., imagining oneself breathing deeply, falling asleep, and having a good night's sleep), and breathing techniques [12].

➢ Sleep hygiene education entails specific information relating to lifestyle (diet, exercise, substance use) and environmental factors (light, noise, temperature) that may interfere with or promote sound sleep. Sleep hygiene education also includes specific sleep facilitating recommendations, such as avoiding visual access to a clock in the bedroom, regular sleep scheduling, avoiding long daytime naps, and limiting alcohol, caffeine, and nicotine intake [28, 33].

Each treatment component consists of an information module (i.e., content and purpose of the specific component), assessment module (i.e., assessment of the severity of the "problem" addressed by the component), application module (i.e., specific information on different types of exercises the participant should engage in), and evaluation module (i.e., assessment of the treatment gain) (Supplementary material 1). Participants are encouraged to complete the information and assessment module in one streak, estimated to last 30–60 min. The application module is then presented gradually over the coming days, and pre-programmed prompts invite the participants to engage in the specific sleep-related exercises over the coming weeks. After completing the prescribed exercises, an evaluation module presents participants with their individualized progress in an exact, readable format, along with suggestions for maintaining the progress. Those individuals who do not seem to experience improvement, based on their response in the evaluation module, are provided (a) practical suggestions on how to engage with the component in different ways and (b) information on how treatment progress may extend over a longer period, why participants are encouraged to continue their engagement in the prescribed exercises. Parallel to completing the treatment components, participants are asked to fill in a sleep diary during the intervention's entire course. Based on the ongoing information from the sleep diary combined with the treatment components, participants receive individualized feedback and instructions (e.g., restricting/increasing time in bed, reminders of disconnecting associations between non-sleep coherent behavior and the bedroom, feedback on relaxation exercises).

App-delivered sleep hygiene education (active control): The sleep hygiene education group is only presented with the sleep hygiene education component in the Hvil® application. Parallel to engaging with this element, participants are asked to fill in a sleep diary during the intervention's entire course.

Criteria for discontinuing or modifying allocated interventions {11b}

If a participant during the trial wishes to terminate the treatment, the participant is withdrawn from the treatment, but will be encouraged to complete all questionnaires and visits as scheduled and will be included in the intention-to-treat analysis.

Strategies to improve adherence to interventions {11c}

The smartphone application Hvil® provides daily notifications. A weekly reminder will be sent to the participants via e-Boks, Denmark's official and secure digital mailbox system reminding them to complete outcome questionnaires. If questionnaires are not responded to in weeks 4, 9, 24, and 52, participants will be contacted by phone by a researcher blinded to treatment allocation.

Relevant concomitant care permitted or prohibited during the trial {11d}

Participants are allowed to continue usual concomitant care for their chronic pain.

Provisions for post-trial care {30}

After the trial, participants randomized to the active control group (sleep hygiene education only) will be offered access to the app-delivered CBT-I intervention in

Hvil®. If participants still express a need for care for their chronic pain and/or insomnia after the trial, they will be advised to contact their general practitioner.

Outcomes {12}

Primary and short-term secondary outcomes will be collected at baseline and weekly for 9 weeks. Medium-term and long-term secondary outcomes will be collected after 24 and 52 weeks. Exploratory physiological sleep metrics from ear-EEG will be collected for five nights at baseline and for 5 nights during week 8.

Primary outcomes

The primary outcomes are the between-group differences (app-delivered CBT-I vs. app-delivered sleep hygiene education) in change from baseline to 9 weeks in insomnia severity assessed with the Insomnia Severity Index (ISI) during the last 14 days [26, 34] and average pain intensity during the last 7 days assessed using a 0–10 numeric rating scale (NRS), with 0 indicating "no pain" and 10 indicating "worst imaginable pain" [25, 35].

Short-term secondary outcomes

- The trajectory of ISI severity scores measured at baseline (T0), mid-intervention at 4 weeks (T1), and post-intervention at 9 weeks (T2).
- Number of patients with more than 30% and 50% improvement, respectively, in ISI severity score from baseline to 9 weeks.
- The trajectory of weekly NRS pain intensity scores measured weekly from baseline to 9 weeks (baseline, week 1, 2, 3, 4, 5, 6, 7, 8, and 9).
- Number of patients with more than 30% and 50% improvement, respectively, in pain intensity from baseline to 9 weeks.
- Perceived effects on sleep using the Global Perceived Effect (GPE) scale after 9 weeks: the participants will respond to the question: "How is your sleep now compared to when you entered this study," with 5 response options (much worse, worse, almost the same/unchanged, improved, and much improved) [36, 37].
- Perceived effects on pain using the Global Perceived Effect (GPE) after 9 weeks: the participants will respond to the question: "How is your pain now compared to when you entered this study," with 5 response options (much worse, worse, almost the same/unchanged, improved, and much improved).
- Sleep quality will be assessed with the Pittsburg Sleep Quality Index (PSQI) [38]. The PSQI consists of 15 multiple choice questions and 4 open-ended questions. The 19 items form the basis a global score. The seven components evaluated by the PSQI are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. Each component has a score ranging from 0 to 3 yielding a total score of 21, with higher scores reflecting worse sleep difficulties.
- Physical and mental health will be assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS-10) Global Health questionnaire version 1.2 [39]. The PROMIS-10 questionnaire comprises 10 items designed to evaluate multiple dimensions of global health. A physical health and mental health score will be calculated from 8 of the 10 questions. The first 9 questions utilize a Likert scale with 5 response options, while the last question assesses pain using a 0–10 numeric rating scale.
- Cognitions about sleep and pain via the 10-item Pain-Related Beliefs and Attitudes about Sleep (PBAS) questionnaire [40] and the 16-item Dysfunctional Beliefs and Attitudes About Sleep (DBAS) questionnaire [41].
- Health-related quality of life via the 5-item (mobility, self-care, usual activities, pain/discomfort, anxiety and depression) EQ5D-5L, the utility index summary measure, and the EQ-5D Visual Analogue Scale (EQ-VAS).

Medium-term secondary outcomes (24-week follow-up)

- ISI severity scores measured at 24-week follow-up.
- Average pain intensity during the last 7 days measured at 24-week follow-up.

Long-term secondary outcomes (52-week follow-up)

- ISI severity scores measured at 52-week follow-up.
- Average pain intensity during the last 7 days measured at 52-week follow-up.
- Health-related quality of life via the 5-item (mobility, self-care, usual activities, pain/discomfort, anxiety and depression) EQ5D-5L, the utility index summary measure, and the EQ-5D Visual Analogue Scale (EQ-VAS) measured at 52-week follow-up.
- Use of sleep and pain medication at 52-week follow-up using data from the prescription database.

- Economic analysis performed at 52-week follow-up. The perspective of the economic analysis in on health care costs. The evaluation will follow the approaches described by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline. Incremental cost-effectiveness ratios will be calculated to determine cost per quality adjusted life year gained, and modeling projections will be made to estimate the long-term cost-effectiveness of the treatment. Data on outpatient visits, admission, and cost per patient contact will be collected from the electronic patient record systems.

Exploratory outcomes

Physiological sleep metrics will be collected as an exploratory outcome and reported in secondary publications. Assessment of physiological sleep metrics will be performed using ear-EEG in a subgroup of 50–60 patients (aiming for app-delivered CBT-I ($n=25$) vs. app-delivered sleep hygiene ($n=25$)). Physiological sleep will be assessed at home for 5 nights at baseline and in week 8 using an ear-EEG research solution (NeuroBuds, T&W Engineering A/S, Lynge, Denmark; Fig. 1) that is custom-fitted for each individual patient. The participants for the ear-EEG subgroup will be included consecutively after inclusion of the first 60 participants among those participants who are eligible for ear-EEG and consent to participate in the ear-EEG measurements. Sleep variables will be derived from the ear-EEG assessments as recommended by the American Academy of Sleep Medicine (AASM) [42] and will include the following sleep metrics among others:

- Total sleep time (TST): the duration from sleep onset to final awakening.
- Sleep efficiency (SE): the ratio of TST to time in bed, expressed as a percentage.
- Sleep onset latency (SOL): the time taken to transition from wakefulness to sleep.
- Wake after sleep onset (WASO): the total duration of wakefulness occurring after initial sleep onset.
- Time in each sleep stage N1, N2, N3, and REM: expressed as a percentage of TST.
- Transition between sleep stages: expressed as a ratio.

Additional baseline data

At baseline, the following data will be collected: demographic data (age, sex, ethnicity, education work status, height, weight, and marital status), pain distribution (pain drawing), medical history, concomitant medicine use.

Participant timeline {13}

The study flow is illustrated in Fig. 2. A time schedule for screening, enrollment, interventions, and outcome assessments is presented in Table 1.

Sample size {14}

Minimal clinical important difference for insomnia severity is 5 points on the ISI [26]. With an estimated SD for change of 2 times the minimal clinical important difference (SD = 10) for patients with chronic pain and insomnia, power of 80%, and an alpha value of 0.05, a minimum of 63 participants in each group is required.

Minimal clinical important difference for pain intensity is 15% [43] corresponding to a change of 1.0 points in this population [44]. With a SD for change of 2.0 for patients with chronic pain and insomnia [44], power of 80%, and an alpha value of 0.05, a minimum of 63 participants in each group is required, considering this test separately. Taking the sequential test principle into account and assuming a non-negative correlation between the two outcomes, the conditional power in the second step is at least 80% and the overall power to demonstrate an effect on pain intensity is at least 64%. The intended analytical approach involves using baseline values as covariates instead of change scores, which is expected to result in a further gain in statistical power. Dropouts may reduce the statistical power; however, as a mixed model will be used for analysis, they will still contribute information. With an expected dropout of 30% [45], we plan to recruit 160 participants (80 for each group).

Stopping rules: This trial has two stopping rules. Inclusion will be terminated on December 31, 2025. If 130 patients have completed the 9-week follow-up before 160 patients have been recruited, the investigators will terminate recruitment of further participants.

Recruitment {15}

Participants will be recruited through advertisements, social media campaigns, and from the pain center waiting list. The anticipated recruitment period is from April 2024 to December 2025.

Assignment of interventions: allocation

Sequence generation {16a}

A data manager not otherwise involved in the project will prepare a computer-generated randomization list with

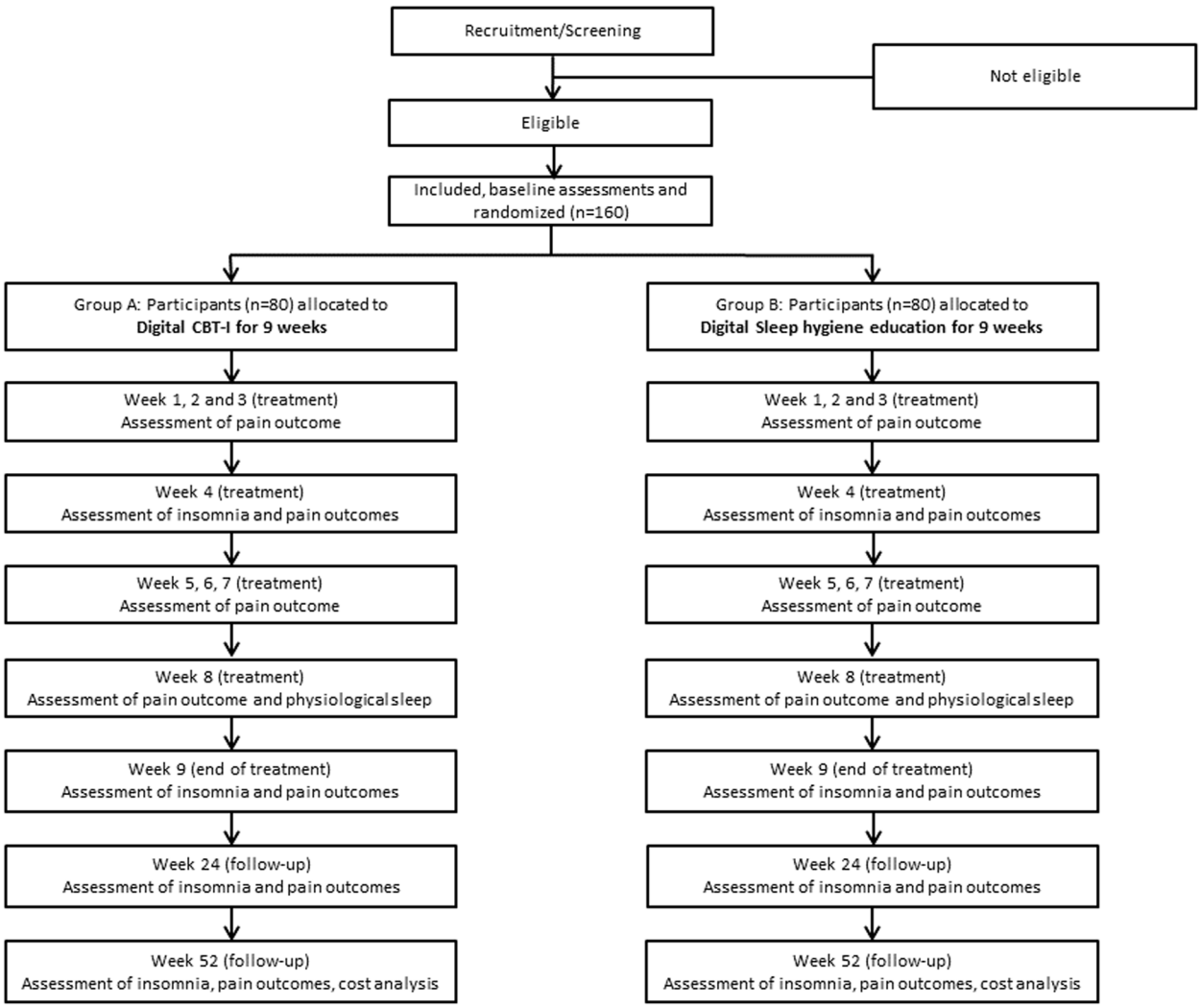

Fig. 2 Overview of the participant flow

160 sequential numbers to either app-delivered CBT-I or app-delivered sleep hygiene education (80 in each arm). The computer algorithm will use permuted-block randomization of 2, 4, and 6 individuals. No stratifications will be applied to the randomization.

Concealment mechanism {16b}

The randomization list will be prepared by a data manager, who has no clinical involvement and is not otherwise involved in the study. The allocation sequence is concealed in a password-protected computer file, which only the data manager has access to.

Implementation {16c}

All participants will be enrolled by the primary investigator MLSO, or a research assistant that has been trained in the study protocol. Each randomized participant will be allocated a sequential number that will randomize them to either the app-delivered CBT-I intervention or the app-delivered sleep hygiene control group.

Assignment of interventions: blinding

Who will be blinded {17a}

The study is single-blinded as investigators are blinded to treatment allocation. Statistical analysts will be blinded to treatment allocation.

Procedure for unblinding if needed {17b}

Unblinding will occur after analysis of the primary outcomes. During the study period, unblinding of a single participant will only occur in case of a medical emergency and if the sponsor/PI finds it necessary to ensure the safety of the participant.

Table 1 Schedule of enrollment, interventions, and outcome assessments

	Study period								
	Enrolment	Allocation	Post-randomization					Follow-up	
Week	-4 - 0	0	1-3	4	5-7	8	9	24	52
Enrolment									
Eligibility	x								
Informed consent	x								
Medical history	x								
Demographic data	x								
Interventions									
Digital CBT-I			x	x	x	x	x		
Digital sleep hygiene			x	x	x	x	x		
Adherence							x		
Outcome assessments									
PROMS									
ISI		x		x			x	x	x
NRS pain intensity		x	x	x	x	x	x	x	x
PSQI		x		x			x		
PROMIS-10 GH		x					x		
PBAS		x		x			x		
DBAS		x		x			x		
GPE							x		
EQ5D		x					x		x
Sleep diary			x	x	x	x	x		
Physiological sleep									
Ear-EEG		x				x			
Adverse device effects		x					x		
Health utilization									x
Medication use									x

ISI Insomnia Severity Index, *NRS* numerical rating scale, *PSQI* Pittsburg Sleep Quality Index, *PBAS* Pain-Related Beliefs and Attitudes about Sleep, *DBAS* Dysfunctional Beliefs and Attitudes About Sleep, *GPE* Global Perceived Effect, *EQ5D* EuroQol 5 dimensions; *PROMIS-10 GH* Patient-Reported Outcomes Measurement Information System Global Health questionnaire v 1.2

Data collection and management

Plans for assessment and collection of outcomes {18a}

Figure 2 and Table 1 describe the plan for enrollment, interventions, and outcome assessments from baseline to the end of treatment after 9 weeks as well as follow-up at 24 and 52 weeks.

The exploratory outcome (physiological sleep metrics) are assessed in a subgroup of approximately 50–60 participants who will have an extra visit before treatment allocation. During this visit, ear-EEG related procedures will be made: molding of customized ear-EEG and initial test of the device, following monitoring of the sleep with the ear-EEG (Fig. 2).

Plans to promote participant retention and complete follow-up {18b}

Participants withdrawing from the study will be encouraged to complete all the scheduled visits and questionnaires.

Data management {19}

Participants will respond to questionnaires via the REDCap electronic data capture tools that enters data directly into the electronic case report file (eCFR). Investigator-collected data will be entered directly into the eCFR during the visits. Range checks for data values will be used to improve the data quality in the eCFR. The ear-EEG data are saved in a secured and logged cloud solution. In the analyzing process, all the data will be transferred to a statistical program. The data will be anonymized and stored 10 years after the end of the trial.

Confidentiality {27}

All personal data related to potential or enrolled participants will be collected in a secure and logged database, SharePoint, or behind double lock if in paper format. Data exports will only include a study-specific identifier. All these precautions will be made to protect confidentiality before, during, and after the trial.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No biological specimens will be collected in this trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

A detailed statistical analysis plan (SAP) will be developed and documented prior to data analysis. The prespecified effectiveness analyses will be based on the intention-to-treat (ITT) principle, which includes all participants that are randomized at baseline. Between-group differences in change from baseline to 9 weeks in the two primary outcomes (ISI score and mean NRS pain in last 7 days, both being continuous variables) between the app-delivered CBT-I group and the app-delivered sleep hygiene education group will be estimated using a mixed linear model approach with ISI and NRS pain intensity as outcomes, time (4 and 9 weeks and 1, 2, 3, 4, 5, 6, 7, 8, and 9 weeks, respectively), treatment arm (app-delivered CBT-I or app-delivered sleep hygiene education), and the interaction between time and treatment arm as fixed effects. Both participant specific intercept and slope will be considered as random effects. The model will be adjusted for ISI score or NRS pain intensity at baseline, respectively. The error variance will be allowed to vary over time and across the two arms. Interactions will be parametrized as time-dependent treatment effects such that the treatment effect at week 9 corresponds directly with the efficacy parameter of interest. The treatment effect will be expressed as the gain in reduction observed in the app-delivered CBT-I arm, i.e., a positive number expresses a favoring of the CBT-I intervention. In the case of missing data during the 9-week trial, repeated measures linear mixed models will take this into account automatically, under the assumption that data is missing at random.

For the statistical assessment of the two primary outcomes (ISI and NRS pain intensity), we will apply a sequential test procedure to compare the effect of the two treatments (app-delivered CBT-I vs. app-delivered sleep hygiene education) on ISI severity in the first step and the effect on NRS pain intensity in the second step. This means that NRS pain intensity as a primary outcome in the second step will only be assessed if statistical significance has been reached in the first step. We use this approach as it seems unlikely that these interventions have direct effect on pain, but rather work through improved sleep. The significance level for the primary outcomes and all secondary outcomes is set to 5%. No adjustment for multiplicity is performed.

In two separate treatment responder analyses, a treatment responder is defined as a patient who reports more than 30% and 50% decrease in ISI and NRS pain intensity after 9 weeks, respectively, and differences between treatment groups will be expressed by adjusted odds ratios. These will be based on logistic regression models including the baseline ISI or NRS pain intensity values and sex as covariates.

Table 2 describes the intended trial interpretation for all possible effect estimates and 95% CI scenarios. A between-group difference of 5 points in the ISI primary outcome is considered clinically relevant. The same principle is applied to the pain intensity with a difference of 1 point to define a clinically meaningful magnitude.

Interim analyses {21b}

No interim analysis will be conducted.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Additional statistical analyses beyond those predefined in this protocol including mediation and effect moderator analyses will be included in the SAP and published in subsequent papers.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Participants in the CBT-I group will be considered "treatment adherent" if they complete 75% or more of the app-delivered CBT-I modules during the study period. Participants in the sleep hygiene group will be considered "treatment adherent" if they have interacted with the sleep hygiene module. A per-protocol analysis will be conducted, including only these treatment adherent participants.

A linear mixed model will be used to analyze all longitudinal outcome measures, including baseline values. This approach enables the inclusion of all randomized participants in the primary analysis, regardless of the pattern of missing data. As a result, the intention-to-treat (ITT) principle can be upheld, provided the assumption that data are missing at random holds true.

To assess the robustness of this assumption, sensitivity analyses will be conducted using multiple imputation methods. Two approaches will be employed. First, a tipping point analysis will be performed by adding a constant value (δ) to all imputed outcome values, simulating a scenario where the true missing values are systematically higher than those expected under the missing at random assumption [46, 47]. The second approach focuses on participants in the app-delivered CBT-I group who discontinue their participation, resulting in missing outcome and adherence data after their last recorded measurement. For these individuals, further outcome increments will be imputed based on the distribution of increments observed in the app-delivered sleep hygiene group among participants with similar outcomes prior to dropout [48].

Table 2 Trial interpretations for the Insomnia Severity Index primary outcome

Scenario	Estimate	Lower bound CI	Upper bound CI	
1.	>=5	>=5		We have demonstrated an intervention effect of clinically relevant magnitude.
2.	>=5	>0		We have demonstrated an intervention effect and obtained a positive intervention effect estimate of clinically relevant magnitude.
3.	>=5	<=0		We obtained a positive intervention effect estimate of clinically relevant magnitude, but we could not demonstrate an intervention effect.
4.	>0, <=5	>0	>=5	We have demonstrated an intervention effect and obtained a positive intervention effect estimate.
5.	>0, <=5	>0	<5	We have demonstrated an intervention effect but also the absence of an intervention effect of clinically relevant magnitude.
6.	>0, <=5	<=0	>=5	We obtained a positive intervention effect estimate, but we could not demonstrate an intervention effect.
7.	>0, <=5	<=0	<5	We obtained a positive intervention effect estimate, but also demonstrated the absence of an intervention effect of clinically relevant magnitude.
8.	<=0		>=5	We obtained a negative intervention effect estimate, but we could not exclude that the intervention effect is of clinically relevant magnitude.
9.	<=0		>0, <5	We obtained a negative intervention effect estimate and demonstrated the absence of an intervention effect of clinically relevant magnitude
10.	<=0		<=0	We have demonstrated the absence of a positive intervention effect.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

The full study protocol and a detailed statistical analysis plan (SAP) will be made publicly available at www.clinicaltrials.gov with the identifier: NCT06361914.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The study is mainly coordinated by the sponsor HBV and the principal investigator (MLSO) with assistance from JBT. There is no trial steering committee.

Composition of the data monitoring committee, its role and reporting structure {21a}

The data monitoring committee (DMC) will be hosted monthly. The DMC will be composed of the sponsor who has clinical pain treatment health professional background, the PI, and one person with a strong trial design and coordination background. The DMC will review safety data, such as AEs in relation to ear-EEG reported by telephone calls or written reports via letter or email by the participants. The DMC will also review the recruitment progress and the quality of the data, such as the data adherence rate and quality of the ear-EEG recordings.

Adverse event reporting and harms {22}

Adverse events (AEs), including adverse reactions (ARs) related to the ear-EEG device, will be documented at every visit. Participants will complete a questionnaire regarding known side effects and will also be interviewed by the investigator about any adverse events that occur throughout the trial. The severity of harms will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All recorded AEs and ARs will be described in detail and documented in the electronic case report form (eCRF).

A serious adverse event (SAE) is defined as any unexpected medical occurrence or effect that, at any dose, results in death, poses a life-threatening risk, necessitates hospitalization or extends an existing hospital stay, causes persistent or significant disability or incapacity, or leads to a congenital anomaly or birth defect. The investigator is required to report all SAEs to the sponsor within 24 h. The causality of an SAE will be determined based on the CT-3 guidelines for collecting, verifying, and presenting adverse event/reaction reports from clinical trials involving medicinal products for human use. In case of harms, the participants are covered by the governmental patient insurance, which includes all patients in the Danish health care system. This insurance will also cover in case of harm from the trial participation.

Frequency and plans for auditing trial conduct {23}

This non-pharmacological clinical trial using a non-CE marked ear-EEG research solution to access sleep metrics in approximately 50–60 participants as an exploratory outcome is notified to the Danish National Center for Ethics (VMK 2314393) under MDR article 82 and does not require GCP monitoring.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committee) {25}

In case of any important protocol amendments, a description of each amendment and its rationale will be reported to the Danish National Center for Ethics.

Dissemination plans {31a}

The protocol and study results will be published in international peer-reviewed journals. All types of results: positive, negative, and inconclusive, will be published. The study results will be disseminated via internet media, social media, written media, news media, patient organizations, and associations. Oral presentation and poster presentation about the study results will be held. The main findings of the study will be published in a publicly available database (e.g., www.clinicaltrials.gov) and the participants will be informed about the study results after publication of the primary results.

Discussion

Chronic pain is one of the most expensive and disabling conditions worldwide with few effective treatments [1]. More than half of those with chronic pain also suffer from insomnia, which can exacerbate the pain condition. Both patients, healthcare professionals, and healthcare policymakers are calling for effective, accessible, and safe treatment options to improve pain and insomnia. Treating insomnia is a promising strategy for relieving chronic pain and the results of the proposed trial have the potential to significantly benefit both patients and society by improving the treatment of two burdensome public health problems—chronic pain and insomnia. It is important to emphasize that treating insomnia in this patient group is crucial not only because it may alleviate pain, but also because addressing insomnia in itself is a valuable goal, as insomnia is associated with substantial negative consequences for function and quality of life. The trial also has the potential to improve the understanding of the mechanisms of action of CBT-I, i.e., are the pain-relieving effects of the treatment directly mediated by changes in physiological sleep metrics using a novel and innovative at-home ear-EEG—or indirectly through changes in patients' cognitions about sleep and pain. The project will produce new knowledge about the effect and mechanism of action for an easily accessible and safe treatment for a patient group with few effective treatment options. Transparency in methodology and outcome measure definitions will be ensured through public access to the trial protocol and prior registration on ClinicalTrials.gov.

Trial status

This RCT began in April 2024 and the process of inclusion is ongoing.

Protocol version 2.0. Date: February 14, 2024.

Approval from the authorities: March 21, 2024.

Start of inclusion: April 12, 2024.

Amendment protocol version 3.0. Date: January 28, 2025.

Amendment approval from the authorities: February 14, 2025.

Expected end of inclusion: December 31, 2025.

Expected end of follow-up: December 31, 2026.

Abbreviations

AE	Adverse events
AR	Adverse reaction
DBAS	Dysfunctional Beliefs and Attitudes about Sleep
eCRF	Electronic case report form
EEG	Electroencephalography
EQ5D	EuroQol 5 dimensions
GPE	Global Perceived Effect
ISI	Insomnia Severity Index
N1	Non-rapid eye movement stage 1
N2	Non-rapid eye movement stage 2
N3	Non-rapid eye movement stage 3
NRS	Numerical rating scale
OPEN	Odense Patient data Explorative Network
PBAS	Pain-Related Beliefs and Attitudes about Sleep
PROMIS-10 GH	Patient-Reported Outcomes Measurement Information System Global Health questionnaire v 1.2
PSQI	Pittsburg Sleep Quality Index
REM	Rapid eye movement
SAP	Statistical analysis plan
SE	Sleep efficiency
SOL	Sleep onset latency
TST	Time from sleep onset until final awakening
WASO	Wake after sleep onset
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-09013-3.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

We acknowledge Open Patient data Explorative Network (OPEN) at Odense University Hospital, Region of Southern Denmark for assisting us with the data collection and management using REDCap electronic data capture tool.

Authors' contributions {31b}

MLSO serves as the principal investigator for this RCT, ensuring continuous coordination, recruitment, randomization, and data collection. MLSO participated in study conceptualization and methodology, manuscript drafting, review, and editing. JBT participated in study conceptualization and methodology, manuscript review, and editing. RZ participated in study conceptualization and methodology, manuscript review, and editing. WV contributed to the statistical analysis and manuscript review and will assist in developing the statistical analysis plan (SAP). LB participated in study conceptualization and methodology, manuscript review, and editing. JJ participated in recruitment, randomization and data collection, manuscript review, and editing. PK participated in study conceptualization and methodology, manuscript review, and editing and will assist in the ear-EEG data analysis. KK reviewed the manuscript and will assist in the cost analysis. HBV is sponsor of this trial and participated in study conceptualization and methodology, manuscript drafting, review, and editing.

Funding {4}

Open access funding provided by University of Southern Denmark Health Insurance Denmark (Sygesikringen "danmark") has granted 2,500,000 DKK to HBV for operating expenses and salary. Region of Southern Denmark PhD fund has granted 628,000 DKK towards salary for the principal investigator MLSO. The Region of Southern Denmark's Fund for Independent and Strategic Research has granted 420,000 DKK to HBV towards operating expenses. The funders do not have any part in the design, conduct, or dissemination of the trial.

Data availability {29}

The trial is investigator-initiated and only the investigators will have access to the dataset.

Declarations

Ethics approval and consent to participate {24}

Danish National Center for Ethics approved the study (VMK 2314393) and data processing in connection with the study has been reported to the region of Southern Denmark's list of on-going research projects via the Executive Secretariat at Odense University Hospital (24/11192). Written, informed consent to participate will be obtained from all participants.

Consent for publication {32}

The informed consent documents provided to participants is provided in Supplementary Material 2.

Competing interests {28}

RZ has taken the initiative to and been actively involved in developing the Hvil® app in collaboration with Enversion A/S, but has no competing financial interests in Hvil®. The remaining authors declare that they have no competing interests. JBT report a research grant worth ~20,000€ from the Novo Nordisk Foundation outside the submitted work. T&W Engineering A/S/Cebreomedical A/S will receive 125,000 DKK to cover their expenses associated with delivery and support of the ear-EEG devices used in this study. Enversion A/S will receive 331,000 DKK to cover their expenses associated with delivery and support of the Hvil® application.

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