

CLINICAL INVESTIGATION PLAN

Digital CBT-I for Patients with Chronic Pain and Insomnia (The Back2Sleep Trial). A Randomized Controlled Trial

NCT06361914

In Danish:

Digital kognitiv adfærdsterapi for insomni (CBT-I) til patienter med kroniske smerter og søvnløshed

Medical device in investigation: Non-CE marked ear-EEG device

The trial will be carried out according to this protocol, National Center for Ethic guidelines, including national regulatory requirements and legislation.

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Confidentiality Statement:

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Medical device: **Non-CE marked ear-EEG research solution** (Data collected in this study is not used for CE marking of this ear-EEG research solution.)

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**Ear EEG-solution
Manufacturer:** **T&W Engineering A/S**
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Summary of protocol changes

Version	Dates	Sections	Change and rationale for change
1.0	xxx	N/A	N/A
2.0	19.02.24	See response to VMK letter	See response to VMK letter
3.0	28.01.2025	<p>Medical device name</p> <p>2. Description and classification of the Ear-EEG research solution</p> <p>3.6.2 Physiological sleep metrics (subgroup of 60 patients)</p> <p>3.5.1 Patient-reported variables</p>	<p>Description of changes/amendments:</p> <p>Ear-EEG research solution (NeuroBuds)</p> <p>Headset/Ear piece</p> <ul style="list-style-type: none"> New jacket on the cable between the two ear pieces (there are no changes in relation to biocompatibility). Fixing the cable in the plugs by pulling the cables through small pouches formed during the modeling (there are no changes in terms of biocompatibility). Adjusted cable routing by rotating the relief 30 degrees (there are no changes in terms of biocompatibility). <p>Recorder</p> <ul style="list-style-type: none"> The firmware of the Recorder unit has been updated to store accelerometer data. <p>Peripheral device</p> <ul style="list-style-type: none"> The list of possible peripheral devices (today a tablet solution) is extended to also include a phone-based solution. The software on the tablet and phone are not considered a medical device and are not under investigation. <p>The changes made to the equipment does not cause any changes in biocompatibility nor in the participant information.</p> <p>At-home questionnaire assessment of pain intensity, insomnia severity and quality of life at week 24 and 52.</p> <p>Reason for changes/amendments:</p> <p>The reason for introducing the changes to the ear-EEG device is to improve the user interface, compliance, and robustness of the solution, as well as to collect accelerometer data to support the study endpoints.</p> <p>The reason for including at-home questionnaire assessment of pain intensity, insomnia severity and</p>

			quality of life at week 24 and 52 is for the cost effectiveness analysis of the Hvil intervention, which was already described in approved version 2, but it was unclear what patient-reported outcomes were assessed at this time-point. It has no influence on the evaluation of the medical ear-EEG device.
		8.1 Conflict of interest and financial support	The study is fully funded by grants from Sygesikringen ‘danmark’ (Health Insurance Denmark) and The Region of Southern Denmark. The funders have no role in the design, conduct or dissemination of the study.

Approval of final clinical investigation plan

I, the undersigned, certify that this clinical investigation will be conducted in accordance with this investigational plan, ethics committee requirements, the Declaration of Helsinki and applicable local governmental regulations.

Henrik Bjarke Vægter
Sponsor

28-01-2025
Date

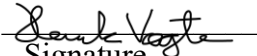

Signature

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Clinical investigation synopsis

Medical device name	Ear-EEG research solution (NeuroBuds)
Medical device in investigation	Non-CE marked ear-EEG device used to monitor sleep before and after cognitive behavioral therapy for insomnia (Data collected in this study is not used for CE marking of this ear-EEG research solution.)
Hvil App NOT classified as medical device	The Hvil app, which aims to guide users in understanding their sleep habits, the factors that affect their sleep, as well as offering tools to establish healthy sleep habits (CBT-I), is not considered a medical device according to the company (Enversion A/S, Aarhus) based on the applicable legislation and guidelines from the Danish Medicines Agency regarding the classification of software and apps as medical devices. The App does not offer medical advice, diagnosis or treatment of sleep-related diseases or conditions, and its features cannot be considered action-oriented in a medical context. The Hvil app is therefore not registered as a medical device in this study.
Study title	Digital CBT-I for Patients with Chronic Pain and Insomnia (The Back2Sleep Trial). A Randomized Controlled Trial.
Principal investigator and study site	PI: Maria Louise Stage Olsen, nurse, MSc, PhD-student Study site: Pain Centre, Department of Anesthesiology and Intensive Care, Odense University Hospital, Heden 7-9, 5000 Odense C.
Study duration	3 years.
Study population	Patients with chronic pain and insomnia.
Number of participants	160 patients / 60 patients with ear-EEG sleep monitoring.
Study design	A randomized clinical superiority trial.
Primary objective	The primary objective is to investigate whether improving sleep is an effective strategy to reduce chronic pain. To do this, we compare the effectiveness of 2 digitally-delivered and commonly used strategies to improve sleep (cognitive behavioral therapy for insomnia (CBT-I) and sleep hygiene education) on sleep and pain in patients with chronic pain and comorbid insomnia.
Secondary objectives	Secondary objectives are to a) explore whether the pain-relieving effect is mediated by a change in physiological markers of sleep quality, b) whether health care cost and use of medications at 12 months are reduced after digital CBT-I, and c) to explore the effectiveness of digital CBT-I compared with sleep hygiene education on:

	<ol style="list-style-type: none"> 1) Physiological sleep metrics (in subsample of 60 patients). 2) Self-reported sleep quality 3) Quality of life. 4) Physical and mental health. 5) Thoughts and beliefs about sleep and pain.
Key endpoints	<p>Pain intensity during the last 7 days: obtained from the 0-10 numerical rating scale (0=no pain and 10=worst imaginable pain).</p> <p>Physiological sleep metrics: Sleep parameters derived from the EEG as recommended by the American Academy of Sleep Medicine (AASM). The sleep parameters include but are not limited to: total sleep time, time in each sleep stage (N1, N2, N3, REM), sleep latency, REM stage latency, wake after sleep onset, sleep efficiency, number of arousals and arousal index and qualitative sleep parameters obtained from sleep diaries.</p> <p>Self-reported sleep parameters: Self-reported sleep quality measured with Insomnia Severity Index (ISI) questionnaire, Pittsburgh Sleep Quality Index (PSQI) and sleep diary (total sleep time and sleep efficiency).</p> <p>PROMs: physical and mental health via the PROMIS-10 Global Health questionnaire and thoughts about sleep and pain via the 10-item Pain-Related Beliefs and Attitudes about Sleep (PBAS) and Dysfunctional Beliefs about Sleep (DBAS) questionnaires.</p>
Key inclusion criteria	<p>For a participant to be eligible, all inclusion criteria must be answered “yes”:</p> <ol style="list-style-type: none"> 1) Age ≥ 18 years. 2) Understand and write Danish. 3) Have smartphone access. 4) Pain for 3 months or longer. 5) Pain must be present on ‘most days’ or ‘every day’ within the past 3 months (will be checked by the question: ‘In the past 3 months, how often did you have pain? – response options: ‘never’; ‘some days’; ‘most days’; ‘every day’). 6) Pain must limit life or work activities on ‘some days’, ‘most days’, or ‘every day’ within the past 3 months (will be checked by the question: ‘In the past 3 months, how often did your pain limit your life or work activities? – response options: ‘never’; ‘some days’; ‘most days’; ‘every day’). 7) Average pain intensity of ≥ 4 on 0-10 Numeric Rating Scale [NRS] in the past 7 days (ranging from ‘no pain’ to ‘worst imaginable pain’). 8) Insomnia symptoms (Insomnia Severity Index (ISI) score > 10; moderate insomnia).

Key exclusion criteria	<p>For a participant to be eligible, all exclusion criteria must be answered “no”:</p> <ol style="list-style-type: none">1) Pregnancy or lactation (Pregnancy is screened for through self-reporting as no risks regarding pregnancy have been identified for the described study procedures).2) Does not have daily access to smartphone/tablet3) Night shift during the time of the CBT-I treatment).4) Currently receiving pharmacological treatment for insomnia (e.g. benzodiazepines, hypnotics ect.).5) Severe psychiatric/somatic illnesses of relevance of their sleep (reported by participant).6) Diagnosed sleep disorders (e.g., OSA, narcolepsy).7) Does not have E-boks.8) Known abuse of alcohol or other substances.9) Suicide and self-damage thoughts (reported by participant).10) People judged incapable, by the investigator, of understanding the participant instruction or who are not capable of carrying through the investigation.11) For the EEG subgroup only (60 patients):<ul style="list-style-type: none">- Age \geq 65 years.- Anatomy of the outer ear making it impossible to do ear-EEG monitoring.- Ear piercings that are not compatible with ear-EEG.- Previous stroke or cerebral haemorrhage and any other structural cerebral disease.- Teeth grinding (bruxism).- Allergic contact dermatitis caused by metals or generally prone to skin irritation.
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List of abbreviations and definitions of terms

AASM = American Academy of Sleep Medicine

ADE = Adverse device effects

AE = Adverse events

CBT-I = Cognitive behavioral therapy for insomnia

CE = Conformité Européene

CHEERS = Consolidated Health Economic Evaluation Reporting Standards guideline

CRF = Case report form

E-CRF = Electronic case report form

EEG = Electroencephalography

GCP = Good Clinical Practice

GCPS-R = Graded Chronic Pain Scale Revised Questionnaire

GDPR = General Data Protection Regulation

GPE = Global Perceived Effect

IB = Investigator's Brochure

ISI = Insomnia Severity Index

ISO = The International Organization for Standardization

N1 = Non-rapid eye movement stage 1

N2 = Non-rapid eye movement stage 2

N3 = Non-rapid eye movement stage 3

NRS = Numeric rating scale

OPEN = Odense Patient data Explorative Network

OSA = Obstructive sleep apnea

PROM = Patient Reported Outcome Measure

PROMIS-10 = Patient-Reported Outcomes Measurement Information System

PSG = Polysomnography

REM = Rapid eye movement

SAP = Statistical analysis plan

SAR = Serious adverse reaction

SE = Sleep efficiency

SOL = Sleep onset latency

SWS = Slow wave sleep

SPT = Sleep period time

TST = Total sleep time from sleep onset until final awakening

WASO = Wake after sleep onset

WHO = World Health Organization

1. Background

1.1 Chronic pain and insomnia

Chronic pain constitutes an increasing health and social burden [1-3]. In 2020, The Danish Health Authority estimated that the annual costs associated with chronic pain are DKK 17.8 billion [3], which exceeds the combined economic burden of heart disease and cancer [4]. According to the World Health Organization Global Burden of Disease study, chronic pain especially back pain is one of the most impacting disabilities worldwide [5]. More than 50% of patients with chronic pain report insomnia [6], and patients with comorbid insomnia often report stronger and widespread pain, compared to those who are sleeping well [7]. In addition, patients with insomnia have higher risk of diabetes, high blood pressure, obesity, cardiovascular disease, stroke, and early death [8]. A few nights with disturbed sleep decreases the pain threshold and impairs the pain-inhibitory function in healthy individuals [9, 10]. Several population-based studies demonstrate a the negative effect of insomnia on pain and report a link between sleep disturbance and chronic musculoskeletal pain several years later [11]. Further, improved sleep quality has been found to be associated with reduced pain 1 year later [12], and a positive correlation between improved sleep and improvement in pain after interdisciplinary pain treatment has been demonstrated [13]. Sleep disturbances are often considered a consequence to chronic pain. This means that insomnia is often overlooked or ineffectively managed with hypnotics or advice on sleep hygiene. While hypnotics may relieve insomnia in the short term, long-term use is not recommended due to side effects, e.g., drowsiness and poor day-time performance, risks of developing dependence and tolerance, and growing concerns regarding possible adverse effects of long-term use of hypnotics, including increased risk of infection, depression, and mortality [14]. Furthermore, hypnotics may adversely affect circadian rhythms in the long term, and a significant proportion of patients who use sleeping pills continue to report poor sleep [15]. Lastly, treatment with addictive drugs is not recommended for people with chronic pain [16]. Therefore, efficacious, easily accessible, and safe pain-relieving alternatives to the current pharmacological treatments for patients with chronic pain and insomnia are needed.

1.2 Cognitive behavioral therapy for insomnia (CBT-I)

Cognitive behavioral therapy for insomnia (CBT-I) is a cost-effective and safe treatment for insomnia [17, 18] and is recommended as first-line treatment [19, 20]. CBT-I is a combination of a combination of the five most commonly used cognitive-behavioral strategies recommended as first choice for treating insomnia by the European Sleep Research Society [21], and the American

Academy of sleep Medicine [22], i.e., sleep restriction therapy, stimulus-control therapy, relaxation/deactivation, cognitive therapy, and sleep hygiene education. Randomized trials of CBT-I have shown beneficial effects not only on sleep efficiency and sleep quality but also on pain immediately after treatment [23] followed by even larger effects 3-12 months after treatment [24, 25]. The effect appears to be partially mediated by changes in maladaptive cognitions about pain and sleep [26], but the mechanism of action is still largely unknown. While highly efficacious, the challenge is to deliver CBT-I to those in need. The main barriers of face-to-face delivered CBT-I are availability of trained therapists, costs, as well as physical and geographical constraints.

1.3 Digital (CBT-I)

Digitally-delivered CBT-I may overcome these constraints, since CBT-I offers an independent, individualized, scalable alternative that can be delivered at home both before, simultaneously or after other pain treatments. Digital CBT-I can be delivered with a smartphone app presenting a combination of the five most commonly used cognitive-behavioral strategies recommended as first choice for treating insomnia (see previous section 1.2). While a meta-analysis of 11 trials has shown digital CBT-I to be highly efficacious in treating insomnia [27], the pain-relieving effect of digital CBT-I has not previously been studied in patients with chronic pain and comorbid insomnia.

1.4 Sleep monitoring in individuals with chronic pain

Polysomnography (PSG) is widely recognized as the gold standard in monitoring of physiological sleep metrics in humans. PSG offers a comprehensive evaluation of sleep patterns, architecture, irregularities in respiration and movement during sleep. Meta-analyses of PSG monitored sleep in chronic pain conditions consistently indicate compromised sleep continuity, a decrease in total sleep time (TST) and in sleep efficiency (SE, the sleep time/time-in-bed ratio) as well as an increase in wake time during the night (wake after sleep onset, WASO) [6]. In addition, changes in sleep architecture, including amounts of slow wave sleep (SWS) has been associated with higher pain intensity in a large population study, and may thus be of particular interest [28]. However, PSG in a sleep laboratory is expensive, not easily accessible and outside the patient's safe environment. PSG often has a significant negative effect on sleep and therefore does not provide a valid representation of the patients "normal sleep". In addition, it requires a healthcare professional to fit the PSG prior to each night and therefore it is not suitable for at-home or long-term sleep monitoring.

1.5 Ear-EEG: a new possibility

To facilitate at-home monitoring of physiological sleep metrics, systems that measure electrical signals from the brain during sleep from electrodes placed in or around the ear (ear electroencephalography (ear-EEG)) have been developed. Among the advanced methods, dry-contact electrodes integrated into personalized earpieces made of soft silicone have shown promising results [29]. The first study utilizing ear-EEG for sleep assessment occurred in 2019, employing custom-made earplugs and a commercially available amplifier [30]. Previous studies have demonstrated the feasibility of measuring EEG in the ear and concluded that ear-EEG compares to conventional scalp-EEG with similar performance [31], and sleep stage classification and sleep-awake patterns have been demonstrated by ear-EEG recordings [30, 32]. Ear-EEG is thus considered a valid measure of sleep metrics [33], is easy to handle and has very little impact on sleep [30, 34] making it convenient for longer recordings. However, monitoring of physiological sleep metrics before and after treatment in patients with chronic pain, has not been performed.

1.6 Objectives

The primary objective of this study is to investigate whether improving sleep is an effective strategy to reduce chronic pain. To do this, we use a randomized controlled clinical superiority trial design to investigate whether digitally-delivered CBT-I has a greater effect on insomnia and pain than commonly delivered sleep hygiene education in patients with chronic pain and comorbid insomnia. Secondary objectives are to a) explore whether the pain-relieving effect is mediated by a change in physiological markers of sleep quality, b) whether health care cost and use of medications at 12 months are reduced after digital CBT-I, and c) to explore the effectiveness of digital CBT-I compared with sleep hygiene education on:

- 1) Physiological sleep metrics (in subsample of 60 patients).
- 2) Self-reported sleep quality.
- 3) Quality of life.
- 4) Physical and mental health.
- 5) Thoughts and beliefs about sleep and pain.

1.6.1 Primary objectives

- Investigate the effectiveness of digitally delivered CBT-I, relative to sleep hygiene education, on difference in changes (Δ baseline-9 weeks) in insomnia symptoms measured on Insomnia Severity Index and pain intensity during the last 7 days measured on a 0-10 numerical rating scale. The objectives are handled in an asymmetric manner, as it seems to be unlikely that CBT-I can have an effect on pain without having an effect on insomnia.

1.6.2 Secondary objectives

- The secondary aim is to explore whether digital CBT-I has a greater effect on Global Perceived Effect (GPE), sleep parameters, maladaptive cognitions about pain and sleep, and health-related quality of life. Furthermore, trajectory (0, 4 and 9 weeks) and responder indices from baseline to 9 weeks will be compared between the treatment groups for the two primary outcomes.
- Explorative aims are to explore changes in physiological sleep metrics, to explore whether the pain relieving effect is mediated by a change in sleep quality or change in maladaptive cognitions about pain and sleep, and whether health care cost and use of medications at 12 months are reduced after digital CBT-I.

1.6.3 Primary and secondary endpoints

1.6.3.1 Primary endpoints

Insomnia: Change in insomnia symptoms during the last 14 days (Δ baseline-9 weeks) obtained from the Insomnia Severity Index (ISI).

Pain intensity: Change in pain intensity during the last 7 days (Δ baseline-9 weeks) obtained from the 0-10 numerical rating scale (0=no pain and 10=worst imaginable pain).

1.6.3.2 Secondary endpoints

Sleep metrics: Sleep parameters derived from the EEG as recommended by the American Academy of Sleep Medicine (AASM). The sleep parameters include but are not limited to: total sleep time, time in each sleep stage (N1, N2, N3, REM), sleep latency, REM stage latency, wake after sleep onset, sleep efficiency, number of arousals and arousal index.

Self-reported sleep from validated sleep questionnaires: PSQI [35] questionnaire and sleep diary.

PROMs: physical and mental health via the PROMIS-10 Global Health questionnaire [36] and thoughts about sleep and pain via the 10-item Pain-Related Beliefs and Attitudes about Sleep (PBAS) and Dysfunctional Beliefs about Sleep (DBAS) questionnaire [37].

2. Description and classification of the Ear-EEG research solution



The intended purpose of the ear-EEG solution is to acquire, record, and transmit electrical brain activity (EEG) of patients 6 years and older. The solution (NeuroBuds) is composed of a Recorder and a Headset. The Recorder is a battery-powered logging device for multiple use. The Headset is an electrode array intended for single patient - multiple use, to acquire electrical activity of the brain (EEG) and accelerometer data using the Recorder. The Headset is composed of two customized earpieces each containing 3 embedded dry electrodes. The electrodes are placed inside the ear canal and in the concha of the ear. In the updated Headset there is a new jacket on the cable between the two ear pieces and the cable has been fixed in the plugs by pulling the cables through small pouches formed during the modeling. The cable routing has been adjusted by rotating the relief 30 degrees (there are no changes in terms of biocompatibility). While the Recorder is charging, EEG data can be transferred from the Recorder to a connected device through a Bluetooth connection. Data will automatically be transferred to T&W Engineering's secured cloud storage when connected to the Internet via the build-in mobile data connection. The list of possible peripheral devices (today a tablet solution) is extended to also include a phone-based solution. The software on the tablet and

phone are not considered a medical device and are not under investigation. See Table 1 for an overview of the manufacturing process and responsibility.

Table 1: Manufacturing of ear-EEG solution		
Step	Process description	Responsible
1	Impression of the participant’s ears and measuring of the length of the participant’s neck size	Odense University Hospital
1	Production of Recorder and individualized Headsets	T&W Engineering A/S

Detailed information about the investigational solution can be found in the Investigator’s Brochure. The Recorder and headset are both a low-risk class I medical device in EU. Data collected in this study is not used for CE marking of this ear-EEG research solution.

2.1 Delivery and support of the ear-EEG system

Recording of EEG during sleep will be performed using a non-CE marked ear-EEG research solution provided by T&W Engineering. T&W Engineering provides and supports the solution throughout the study period, including ongoing firmware updates to ensure data quality. Components that break during the study will be replaced. All Recorders and Headsets will be returned to T&W Engineering when they are no longer needed, breaks, or need firmware update.

2.2 Traceability and accountability of the investigational device

The earpieces are labelled with lot/serial numbers for subsequent tracing and identification. At the site, a device accountability system will be maintained during the study and afterwards, documenting device shipment and receipt, storage at the site, use, and return as applicable.

2.3 Necessary training

All investigators will be trained in the use of the ear-EEG solution prior to initiation of the study. This includes customization of earpieces, mounting of earpieces, and setting up and downloading data from the ear-EEG solution.

2.4 The Hvil App

The Hvil App is NOT classified as medical device: The Hvil app, which aims to guide users in understanding their sleep habits, the factors that affect their sleep, as well as offering tools to establish healthy sleep habits is not considered a medical device according to the company (Enversion A/S) based on the applicable legislation and guidelines from the Danish Medicines Agency regarding the classification of software and apps as medical devices. The App does not offer medical advice, diagnosis or treatment of sleep-related diseases or conditions, and its features cannot be considered action-oriented in a medical context. The Hvil app is therefore not registered as a medical device in this study.

3. Methods

3.1 Study Time plan

Expected submission for approval from authorities: 14.12.2023

Expected start of inclusion: 01.03.2024

Expected end of inclusion: 29.12.2025

Expected end of follow-up: 28.02.2026

Expected submission of papers: 31.12.2026

3.2 Study design

This study aims to investigate the efficacy of digital CBT-I for improving sleep (i.e. reducing insomnia severity) and reducing pain intensity in patients with chronic pain and comorbid insomnia. To achieve this goal, we will perform a randomized controlled single-blind clinical superiority trial. Participants will be randomized with an allocation 1:1 ratio into a digital CBT-I group and a sleep hygiene education group. Both groups will use the Hvil app, but the amount of content will be different. Using a data manager not affiliated with the project through the Open Patients data Exploratory Network (OPEN) at Odense University Hospital, the randomization can be implemented in the program REDCap. The data manager will prepare the randomization list in REDCap. Patients responding to study advisements will after their initial phone contact be invited to a clinical visit at the Pain Center at Odense University Hospital (visit 1) for study information, assessment of eligibility and signing of informed consent. Patients consenting to participate and matching the eligibility criteria will be invited for a visit 2, where the final decision on inclusion

will be made. Included patients will then have baseline assessments performed and be randomized. The trial period is 9 weeks (compliance assessment in week 4 by phone) (Figure 1).

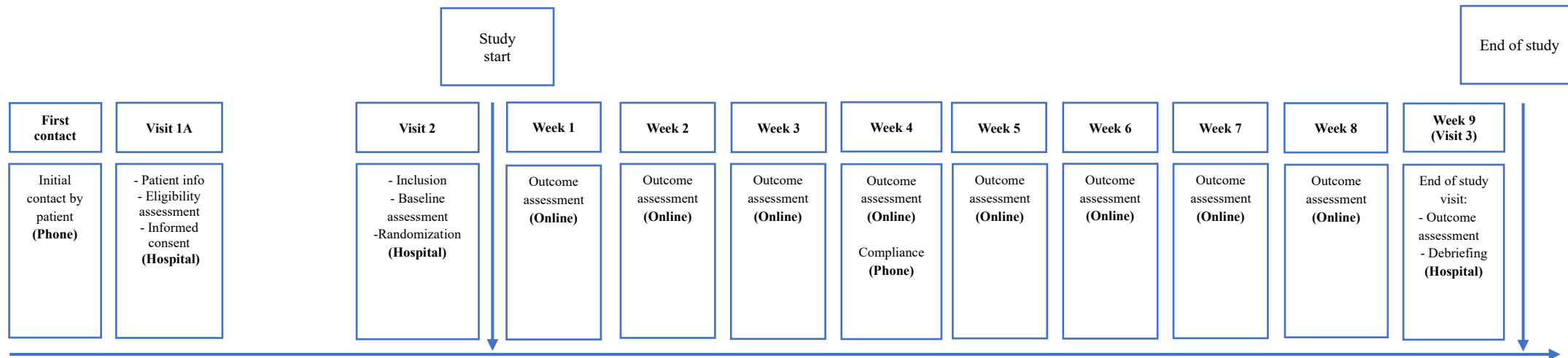


Figure 1A. Study overview for 100 participants without ear EEG: A description of expected time frame for the individual patient.

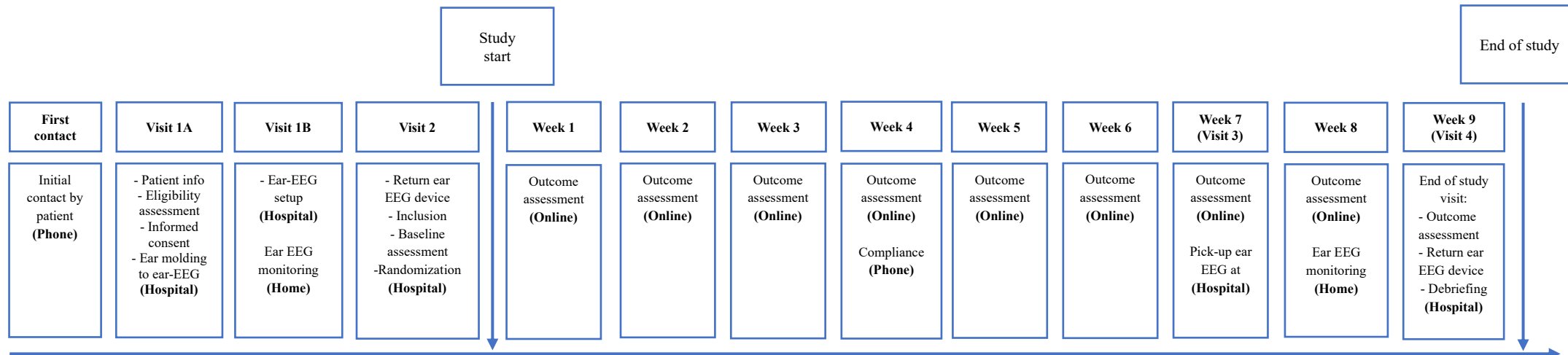


Figure 1B. Study overview for 60 participants with ear EEG: A description of expected time frame for the individual patient.

3.3 Study procedures and study visits

Detailed description of procedures and study visits:

First contact (phone):

- Interested subjects contact the PI at Smertecenter Syd by telephone after they have seen an advertisement for the study. There is no unsolicited contact by the PI.
- To ensure that interested subjects, who certainly do not meet the criteria to participate in the study, do not have to spend unnecessary time and resources coming to a physical meeting with oral information about the study, the eligibility criteria (see section 5.2 and 5.3 for in-/exclusion criteria) are assessed over the phone.
- Written information (Deltagerinformation) is send to potentially eligible subjects' e-boks.
- Appointment for eligibility visit 1A if subject is potentially eligible.

Eligibility assessment (physical visit 1A):

- Oral study information and time for questions.
- Eligibility criteria.
- Informed consent.
- Ear measurement for individual molding of ear electroencephalography (EEG) device (subgroup of 60 patients). See section 3.6.2 for specific procedures on ear EEG.

Ear EEG setup (physical visit 1B – subgroup of 60 patients):

- Instruction and handing out ear EEG to patients.
 - Start 7-day adaption period for sleeping with ear EEG (2 days with; 1 day without; 2 days with; 2 days without).
 - After 7-day adaptation period – First week of EEG sleep baseline assessment (5 out of next 7 days).
- (There must be 14 days between physical visit 1B and physical visit 2 to allow for adaptation period and baseline EEG measurement).

Inclusion, baseline testing and randomization (physical visit 2):

- Study inclusion.
- Demographic data collection.

- Primary outcomes (insomnia and pain).
- All other PROMs.
- Randomization.
- Participant is setup in Hvil[®] app

Outcome assessment (Week 1):

- Pain intensity.

Outcome assessment (Week 2):

- Pain intensity.

Outcome assessment (Week 3):

- Pain intensity.

Outcome and safety assessment (Week 4 - phone):

- Primary outcomes (insomnia and pain).
- Questionnaire on sleep quality
- Phone call for compliance assessment.

Outcome assessment (Week 5):

- Pain intensity.

Outcome assessment (Week 6):

- Pain intensity.

Outcome assessment (Week 7 - phone):

- Pain intensity.
- Remind 60 patients EEG subgroup to start follow-up EEG sleep assessment in week 8

Outcome assessment (Week 8):

- Pain intensity.
- EEG sleep follow-up assessment (5 out of next 7 days) - subgroup of 60 patients.

Outcome assessment (Week 9 – physical visit 3):

- Primary outcomes.
- All other PROMs.
- Return ear EEG device (60 patient subgroup).
- Debriefing

Outcome assessment (Week 24 and 52 – long-term follow-up at home):

- Insomnia Severity Index and pain intensity last 7 days.
- EQ5D questionnaire (quality of life)

3.4 Primary and secondary outcomes

3.4.1 Primary outcomes

- Insomnia symptoms. Difference in change between treatment groups from baseline to 9 weeks. Insomnia will be assessed with the Insomnia Severity Index (ISI), which is a brief 7 item patient-reported instrument with a score ranging from 0-28 (0=best;28=worst) [35, 38].
- Average pain intensity during the last 7 days. Difference in change between treatment groups (digital CBT-I vs. sleep hygiene education) from baseline to 9 weeks (pain intensity at baseline minus pain intensity at 9 weeks). Average pain intensity during last 7 days will be assessed on a 0-10 Numeric Rating Scale (NRS) (ranging from ‘no pain to ‘worst imaginable pain’) [39].

3.4.2 Secondary outcomes

- The trajectory of ISI severity scores from baseline over 4 weeks to 9 weeks.
- Number of patients with clinically relevant improvement in ISI severity score from baseline to 9 weeks.
- Number of patients with insomnia at 9 weeks. Insomnia will be defined according to described cut-offs.
- The trajectory of weekly NRS pain intensity scores (primary outcome) from baseline to 9 weeks [39].

- Number of patients with more than 30% improvement in the primary outcome from baseline to 9 weeks (Number of responders are calculated for both the CBT-I and the sleep hygiene education group) [40].
- Number of patients with more than 50% improvement in the primary outcome from baseline to 9 weeks (Number of responders are calculated for both the CBT-I and the sleep hygiene education group).
- Global Perceived Effect (GPE). Assessment of overall change in pain from baseline to 9 weeks. Participants will be asked at 9 weeks: 'How is your back pain now compared to when you entered this study', with 5 response options (much worse, worse, almost the same/unchanged, improved, much improved) [41].
- Sleep Quality: Sleep quality will be assessed with the Pittsburgh Sleep Quality Index (PSQI), which is developed to provide a reliable, valid and standardized measure of sleep quality. The PSQI consists of 19 items with 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 [42].
- Physical and Mental Health will be assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS-10) Global Health questionnaire version 1.2 [43]. Difference in change in physical and mental health scores between treatment groups from baseline to 9 weeks. PROMIS-10 consist of 10 questions concerning different aspects of global health. The first 9 questions are score on a Likert scale with 5 response options, and the last question asks about pain using a 0-10 numeric rating scale.
- Sleep diary (total sleep time and sleep efficiency) implemented in the Hvil[®] app.
- Thoughts about sleep and pain via the Pain-Related Beliefs and Attitudes about Sleep (PBAS) questionnaire [37]. Differences in change in thoughts about sleep and pain scores between treatment groups (digital CBT-I vs. sleep hygiene education) from baseline to 9 weeks. PBAS consist of 10 item questions.
- Thoughts about sleep via the Dysfunctional Beliefs and Attitudes About Sleep (DBAS) Questionnaire [44]. Differences in change in thoughts about sleep scores between

treatment groups (digital CBT-I vs. sleep hygiene education) from baseline to 9 weeks. DBAS consists of 16 questions.

Exploratory outcomes:

- Physiological sleep (subgroup of 60 patients). Difference in change in sleep metrics between treatment groups (digital CBT-I [n=30] vs. sleep hygiene education [n=30]) from baseline to 8 weeks. The following sleep metrics will be assessed using ear EEG: sleep period time (SPT); time from sleep onset until final awakening (TST); sleep efficiency (SE) which is the ratio of TST to time in bed / 100%; sleep onset latency (SOL); wake after sleep onset (WASO), wake time within the SPT. The following sleep architecture variables will be used: REM sleep latency, time from sleep onset until first epoch of REM stage sleep; amount of wake and stage N1, N2, N3, and R sleep as a percentage of SPT; number of awakenings within TST; arousal index which is number of arousals per hour.

Cost effectiveness:

- Analysis of health costs will be performed at 12-month follow-up and the economic 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 longer term cost-effectiveness of the treatment. Analysis of medication use will be performed using data from the prescription database.

3.5 Data variables

3.5.1 Patient-reported variables

The following questions and questionnaires will be used during screening and eligibility assessment in visit 1:

- **Age:** Age will be assessed based on date of birth.
- **Chronic pain:** Chronic pain will be assessed using the Graded Chronic Pain Scale Revised (GCPS-R) questionnaire. The GCPS-R is a brief, freely available questionnaire that assesses frequency and severity of pain and its impact. The GCPS-R uses 5 items to categorize pain into no chronic pain, mild chronic pain, bothersome chronic pain, and high-impact chronic pain [45] (see Appendix 2).

- **Pain intensity rating:** Item 3 in the Graded Chronic Pain Scale Revised (GCPS-R) questionnaire will be used to assess average pain intensity during the last 7 days. Item 3 is an 11-point numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain) [46], which has been shown to be reliable and valid [47] (see Appendix 2).
- **Insomnia:** Insomnia will be assessed with the Insomnia Severity Index (ISI) which encompasses seven items measuring severity of sleep-onset; sleep maintenance and early morning awakening difficulties; satisfaction with sleep patterns; daily function interference; impairments due to sleep problems; and distress or concerns due to sleep problems [38]. Each item is rated from 0 to 4 (0 = no problem, 4 = severe problem), yielding a total score of 28, with higher scores reflecting worse insomnia, and is validated for use in research [48] (see Appendix 5a).

The following data will be recorded in the electronic case report form (eCRF) after consent at visit 1:

- Date of birth
- Sex
- E-mail (used to set-up user in Hvil app)
- Ethnicity
- Height
- Weight
- Marital status
- Level of education
- **EQ-5D-5L:** EQ-5D is a standardized measure of health-related quality of life often used to derive QALYs for application in cost-effectiveness evaluations. The EQ-5D comprises five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression as well as the EQ-5D visual analogue scale (EQ VAS) (see Appendix 1).
- **The Graded Chronic Pain Scale Revised (GCPS-R)** (see Appendix 2).
- **Pain intensity rating and pain distribution:** Item 3 in the Graded Chronic Pain Scale Revised (GCPS-R) questionnaire will be used to assess average pain intensity during the last 7 days. Item 3 is an 11-point numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain) [46], which has been shown to be reliable and valid [47] (see Appendix 2). Furthermore, participants will complete pain drawings indicating all pain

locations – divided into 71 body areas – with pain during the previous week [49] (see Appendix 2 and Appendix 4).

- **Insomnia:** Insomnia will be assessed with the Insomnia Severity Index (ISI) which encompasses seven items measuring severity of sleep-onset; sleep maintenance and early morning awakening difficulties; satisfaction with sleep patterns; daily function interference; impairments due to sleep problems; and distress or concerns due to sleep problems [38]. Each item is rated from 0 to 4 (0 = no problem, 4 = severe problem), yielding a total score of 28, with higher scores reflecting worse insomnia, and is validated for use in research [48] (see Appendix 5a).
- **Sleep Quality:** Sleep quality will be assessed with the Pittsburg Sleep Quality Index (PSQI), which is developed to provide a reliable, valid and standardized measure of sleep quality. The PSQI consists of 19 items with 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 [42] (see Appendix 5b).
- **Pain-Related Beliefs and Attitudes about Sleep (PBAS):** PBAS is used for assessment and treatment of insomnia comorbid with chronic pain [37]. PBAS consists of 10 questions that assesses patients' beliefs about the interaction between pain and sleep. All questions are completed using a 0-10 numeric rating scale between 0 “strongly disagree” and 10 “strongly agree”. The total score is the average score of all items, with a higher average score indicating stronger or more inflexible beliefs that pain and sleeplessness are linked (see Appendix 6a).
- **Dysfunctional Beliefs and Attitudes about Sleep (DBAS):** DBAS is used to assess various sleep/insomnia-related cognitions. DBAS consists of 16 questions that assesses patients' beliefs, attitudes, expectations, appraisals, attributions about sleep. All questions are completed using a 0-10 numeric rating scale between 0 “strongly disagree” and 10 “strongly agree”. The total score is the average score of all items, with a higher average score indicating more dysfunctional beliefs about sleep (see Appendix 6b).
- **Physical and Mental Health:** assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS-10) Global Health questionnaire version 1.2 [43]. Difference

in change in physical and mental health scores between treatment groups from baseline to 9 weeks. PROMIS-10 consist of 10 questions concerning different aspects of global health. The first 9 questions are score on a Likert scale with 5 response options, and the last question is asking about pain using a 0-10 numeric rating scale (see Appendix 3).

- **Medical history and concomitant illnesses:** Self-reported medical history and concomitant illnesses relevant to the investigation will be recorded in the eCRF by a trained study nurse during the information visit. A clinically significant worsening of a concomitant illness will be reported as an AE (see section 7 on study safety).
- **Concomitant medication:** Self-reported concomitant medication will be recorded in the eCRF by a trained nurse during the information visit. Changes in concomitant medication will be recorded at each visit as they occur.

The following questions and questionnaires will be completed during the study (see Table 2):

- **Pain intensity rating (weekly for 9 weeks, at week 24 and 52):** Average pain intensity during the last day and current pain intensity in the morning will be assessed on an 11-point numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst imaginable pain) [46] (see Appendix 2).
- **Insomnia (baseline, week 4, week 9, week 24 and 52):** Insomnia will be assessed with the Insomnia Severity Index (ISI) which encompasses seven items measuring severity of sleep-onset; sleep maintenance and early morning awakening difficulties; satisfaction with sleep patterns; daily function interference; impairments due to sleep problems; and distress or concerns due to sleep problems [38]. Each item is rated from 0 to 4 (0 = no problem, 4 = severe problem), yielding a total score of 28, with higher scores reflecting worse insomnia, and is validated for use in research [48] (see Appendix 5).
- **Sleep Quality:** Sleep quality will be assessed with the Pittsburgh Sleep Quality Index (PSQI), which is developed to provide a reliable, valid and standardized measure of sleep quality. The PSQI consists of 19 items with 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 [42] (see Appendix 5b).

- **Pain-Related Beliefs and Attitudes about Sleep (PBAS) (baseline, week 4 and week 9):** PBAS is used for assessment and treatment of insomnia comorbid with chronic pain [37]. PBAS consists of 10 questions that assesses patients' beliefs about the interaction between pain and sleep. All questions are completed using a 0-10 numeric rating scale between 0 "strongly disagree" and 10 "strongly agree". The total score is the average score of all items, with a higher average score indicating stronger or more inflexible beliefs that pain and sleeplessness are linked (see Appendix 6a).
- **Dysfunctional Beliefs and Attitudes about Sleep (DBAS):** DBAS is used to assess various sleep/insomnia-related cognitions. DBAS consists of 16 questions that assesses patients' beliefs, attitudes, expectations, appraisals, attributions about sleep. All questions are completed using a 0-10 numeric rating scale between 0 "strongly disagree" and 10 "strongly agree". The total score is the average score of all items, with a higher average score indicating more dysfunctional beliefs about sleep (see Appendix 6b).
- **Physical and Mental Health (baseline and week 9):** Assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS-10) Global Health questionnaire version 1.2 [43]. Difference in change in physical and mental health scores between treatment groups from baseline to 9 weeks. PROMIS-10 consist of 10 questions concerning different aspects of global health. The first 9 questions are score on a Likert scale with 5 response options, and the last question is asking about pain using a 0-10 numeric rating scale (see Appendix 3).
- **Sleep diary (weekly):** Sleep diary is completed daily as part of the Hvil[®] app.
- **Ease-of-use and Comfort Questionnaire (visit 1B and week 8):** The questionnaire is only completed in subsample of 60 patients during weeks with ear EEG (see Appendix 7).
- **EQ-5D-5L (baseline, week 9, week 24 and 52):** To analyze quality adjusted life years (see Appendix 1).

3.5.2. Sleep metrics from Ear EEG

Sleep metrics will be derived from the EEG assessments as recommended by the American Academy of Sleep Medicine (AASM) [50]. The following sleep parameters will be assessed using ear EEG: sleep period time (SPT); time from sleep onset until final awakening (TST); sleep efficiency (SE) which is the ratio of TST to time in bed / 100%; sleep onset latency (SOL); wake after sleep onset (WASO), wake time within the SPT. The following sleep architecture variables

will be used: REM sleep latency, time from sleep onset until first epoch of REM stage sleep; amount of wake and stage N1, N2, N3, and R sleep as a percentage of SPT; number of awakenings within TST; arousal index which is number of arousals per hour.

Data quality: The data quality is of high importance in the assessment of the ear-EEG system. Data quality depends on how much of the recording is left after data rejection. At channel rejection, the electrodes with loose or unstable connections to the skin are identified and excluded from the data set. At epoch rejection, time periods are identified in which the signal is dominated by either temporary movement of the ear plug, EMG artifacts from muscle activity, or other artifacts.

3.5.3. Data from medical journals

No data from medical journals will be collected for this study.

3.5.4. Handling of biological material

No biological material will be collected for a bio bank or other research purposes.

3.6 Description of specific assessment procedures

3.6.1 Patient-reported outcomes:

All patient-reported outcomes will be collected using an online questionnaire administered through REDCap, which ensure data logging and comply with all demands from the Danish Data Protection Agency regarding data security. For timing of collection of patient-reported outcomes please refer to section 3.3.

3.6.2 Physiological sleep metrics (subgroup of 60 patients)

After inclusion of the first 60 patients, 60 patients will be selected for objective assessment of sleep. Assessment of changes in sleep metrics will be performed during two 5 of 7-day periods. One period at baseline prior to initiation of study treatment (between visit 1B and visit 2) and one period in week 8. The assessment will be performed using a non-CE marked ear-EEG research solution (T&W Engineering A/S, Lynge, Denmark) that is custom-fitted for each individual patient. The Recorder and headset are both a low-risk class I medical device in EU. Data collected in this study is not used for CE marking of this ear-EEG research solution. T&W Engineering provides and supports the solution throughout the study period, including ongoing firmware updates to ensure

data quality. Components that break during the study will be replaced. All Recorders and Headsets will be returned to T&W Engineering when they are no longer needed, breaks, or need firmware update. Prior to the actual assessment each individual patient will have a custom-fit earplug moulded, which will hold the EEG electrodes. Furthermore, patients will be instructed in the use of the system. Previous studies have demonstrated the feasibility of measuring ear EEG in patients own home and shown that ear-EEG compares to conventional scalp-EEG (i.e. used in polysomnography assessment of sleep) with similar performance.[30, 51] Sleep variables will be derived from the EEG assessments as recommended by the American Academy of Sleep Medicine (AASM) [50]. The intended purpose of the ear-EEG solution is to acquire, record, and transmit electrical brain activity (EEG) of patients 6 years and older. The solution is composed of a Recorder and a Headset. The Recorder is a battery-powered logging device for multiple use. The Headset is an electrode array intended for single patient - multiple use, to acquire electrical activity of the brain (EEG) and accelerometer data using the Recorder. The Headset is composed of two customized earpieces each containing 3 embedded dry electrodes. The electrodes are placed inside the ear canal and in the concha of the ear. All investigators will be trained in the use of the ear-EEG solution prior to initiation of the study. This includes customization of earpieces, mounting of earpieces, and setting up and downloading data from the ear-EEG solution. The earpieces are labelled with lot/serial numbers for subsequent tracing and identification. At the site, a device accountability system will be maintained during the study and afterwards, documenting device shipment and receipt, storage at the site, use, and return as applicable. Detailed information about the investigational solution can be found in the Investigator's Brochure.

Study procedures related to ear EEG:

(Physical visit 1A): Ear measurement for individual molding of ear electroencephalography (EEG) research solution:

- Ear impression for individualization of the Headset. Ear measurement is performed by a trained person (medical doctor or study nurse) on site. From the impression, personal earbuds to the Headsets are produced.

Ear EEG setup (physical visit 1B):

Instructions and handing out ear-EEG solution to patients. When handing out the Headset a visual inspection is performed to assess the quality of the earbud fit. A short recording will

be made in order to train the patient in recording and downloading of data to a tablet or phone. During the recording the patient is asked to close the eyes, blink, move the eyes rapidly and relax.

- Additionally, the participant's capability of mounting the earpieces autonomously and uploading data to the external device will be assessed. Furthermore, a training session of completing sleep diary, pain questions and ease-of-use and comfort questionnaire will be completed.

Getting accustomed to repeated ear EEG use (Between visit 1B and visit 2 – home)

- Start 5-day adaption period for sleeping with ear EEG (2 days with; 1 day without; 2 days with). The participant will be sent home with the equipment and asked to sleep with it on the following 2 nights, followed by one night without the device followed by another 2 nights sleeping with the device. This phase is to allow the participant to get accustomed to wearing the device during several nights. The participants are also asked to upload the recorded data each morning to the cloud and recharge the Recorder.

Pre-intervention Ear EEG assessment (Between visit 1B and visit 2 – home)

- After 5-day adaptation period – First week of EEG sleep assessment (5 out of next 7 days). The participant will be asked to sleep with the ear-EEG device for 5 nights in the following week. Participants are encouraged to maintain normal sleeping habits. The participant will upload recordings to provided tablet or phone every day. In case of low compliance with EEG recordings or data upload the investigators will contact the participant, clarify and provide necessary support.

During-intervention ear EEG assessment (Week 7 and Week 8 – home)

- The participant will be asked to pick-up the ear EEG at Odense University Hospital during week 7, and sleep with the ear EEG device for 5 nights during week 8. Participants are encouraged to maintain normal sleeping habits. The participant will upload recordings to provided tablet or phone every day. In case of low compliance with EEG recordings or data upload the investigators will contact the participant, clarify and provide necessary support.

Return ear EEG solution (Week 9 – physical visit 3):

- Return ear EEG solution. The participant return to the study site for an end of study visit to return the ear-EEG solution.
- Registration of adverse device events and completion of the Summative. The PI will explore and register any adverse device events, and ease-of-use and comfort using Ease-of-use and Comfort questionnaire and System Usability Scale.

Optional phone visits during the two ear EEG weeks:

- In case of error on the uploaded ear-EEG data the project personal will contact the participant by phone to correct the data collection and data upload.

Table 2: Detailed overview of timing of outcomes and assessments.

[illegible]

Long term cost-effectiveness is evaluated with online questionnaires at home after 24 and 52 weeks using pain intensity, ISI and EQ5D.

3.7 Measures for reduction in bias

A data manager, otherwise, not involved in the study, will prepare the randomization list, using a computerized algorithm. After inclusion, participants will receive an unique randomization key to impute in the Hvil® app according to the abovementioned procedure to receive either digital CBT-I or sleep hygiene education for 9 weeks. All patient reported data will be filled in directly to the eCRF via an online questionnaire using REDCap. Statistical analyses will be blinded to treatment allocation.

3.8. Data management

The collected data are protected in accordance with the “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). Data management is the responsibility of the investigators (Odense University Hospital and Aarhus University) but may be delegated under an agreement of transfer of responsibilities to T&W Engineering A/S. Data from the eCRF will be stored electronically on secured servers at Region Syddanmark after last patient last visit. Data exchange with collaborators will happen through a secure data sharing service. All data will be saved for 10 years after last data entry and closure of database, at which point the ID number list is deleted.

3.8.1. Participant identification and confidentiality

Participants will be assigned a unique study identification number upon enrolment in the study. The investigator will maintain a list identifying all participants entered into the study. All data will be handled in a way that protects the participant’s confidentiality and anonymity.

3.8.2. Source data

Source documents in this study are 1) the original eCRF documents from which the data in the database is obtained and 2) raw sleep metrics from ear-EEG. eCRFs and raw sleep metrics will be archived electronically and made available for regulatory authorities upon request for evaluation of study progress, safety and data validity.

3.8.3. Electronic case report forms (eCRF)

Demographics and questionnaire data will be collected and recorded in the eCRFs. eCRFs are provided in a uniform design, each form heading identifies the participant, and each visit will be

dated. Completed eCRFs will be reviewed and signed by the investigator. eCRFs are confidential documents and will only be available to the investigator, involved site staff, data management personnel, and if requested, to the ethics committee or regulatory authorities, the Danish Medicines Agency. In case of errors, omission or discrepancies found in the eCRF, a query will be sent to the investigator. The eCRF will be corrected as required and the corrected data entered into the database. In case of system break down, all data will be collected in a paper version similar to the eCRF version. This data will be entered into the eCRF as soon as the break down has been resolved. Any source data in paper format will be archived in the trial master file.

3.8.4. Ear EEG data

Ear EEG data will be saved pseudo-anonymized in a data system at Aarhus University to which relevant personnel at the site will have access. Data will be uploaded and transferred to the designated data system by the participant on daily basis. Missing data at the recording level, for instance malfunctioning electrodes will be represented by NaN-values, meaning that the data analysis will, largely, ignore such data points. Missing data at participant level, such as a participant being represented by fewer recordings than others, will not particularly influence the analysis of the given participant. Any estimates from that participant will, however, be treated as more uncertain than those from more well-described participants.

4. Randomization and description of sleep treatments

4.1 Randomization

Participants will be randomized with an allocation 1:1 ratio into a sleep hygiene education group (usual care for patients with chronic pain and sleep problems) and a digital CBT-I group. Both groups will use the Hvil app, but the amount of content will be different. A data manager not otherwise involved in the project will prepare a computer-generated randomization list with 160 sequential numbers to either digital CBT-I or 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.

Both treatment arms will be delivered using the smartphone application Hvil[®], which are also used in other studies on treatment of insomnia (e.g. NCT05561829). This platform is used for both treatments to ensure that only the amount of contents is different and the form of delivery. The Hvil

App is not classified as medical device. The Hvil app can guide users in understanding their sleep habits, the factors that affect their sleep, as well as offering tools to establish healthy sleep habits. Participants can continue their usual care during the trial.

4.2 Sleep hygiene education

Sleep hygiene education is the commonly delivered treatment for insomnia in patients with chronic pain. The digital sleep hygiene education treatment in Hvil® includes the sleep hygiene education element that 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 [52, 53]. Parallel to engaging with this element, participants are asked to fill in a sleep diary during the intervention's entire course.

4.3 CBT-I

CBT-I is the recommended treatment for insomnia, but is often not delivered to patients with chronic pain and comorbid insomnia as the focus is mainly on the pain condition. The digital CBT-I intervention in Hvil is designed to be completed over a period of nine 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 [54, 55] including five treatment components:

- **Sleep restriction** includes behavioral instructions to limit the time spent in bed to increase sleep drive and further reduce time awake in bed. The aim is to increase SE (i.e., $\text{total sleep time (TST)} / \text{total time in bed (TIB)} \times 100\%$). Initially, bedtime is restricted to the average TST reported in a two-week sleep diary and then titrated to achieve a SE >85% with the optimal TST [53, 56].
- **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 [53, 57].

- **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 [58].
- **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 [59]. These misconceptions are modified and replaced by realistic alternatives using cognitive restructuring techniques [60].
- **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 [52, 53].

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). Participants are encouraged to complete the information and assessment module in one streak, estimated to last 30-60 minutes. 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 in 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)

4.4 Rules for termination of the study

The study will be terminated when all recruited participants have completed their final follow-up (last patient – last visit). As the study use an already marketed treatment application, we expect no treatment related serious adverse responses.

5. Study population

5.1 Definition of the overall participant population

Participants eligible for this study are individuals with chronic pain and insomnia in compliance with the inclusion/exclusion criteria listed below. The health status of the participants is assessed by self-reports. Inclusion and exclusion criteria ensure generalizability of study results for a broad population of individuals with chronic pain and insomnia, and only serious concomitant conditions, which could interfere with the study procedures should prevent participants from entering the study.

5.2 Inclusion criteria

For a participant to be eligible, all inclusion criteria must be answered “yes”:

- Age \geq 18 years.
- Understand and write Danish.
- Have smartphone access.
- Pain for 3 months or longer.
- Pain must be present on ‘most days’ or ‘every day’ within the past 3 months (will be checked by the question: ‘In the past 3 months, how often did you have pain? – response options: ‘never’; ‘some days’; ‘most days’; ‘every day’).
- Pain must limit life or work activities on ‘some days’, ‘most days’, or ‘every day’ within the past 3 months (will be checked by the question: ‘In the past 3 months, how often did your pain limit your life or work activities? – response options: ‘never’; ‘some days’; ‘most days’; ‘every day’).

- Average pain intensity of ≥ 4 on 0-10 Numeric Rating Scale [NRS] in the past 7 days (ranging from 'no pain' to 'worst imaginable pain').
- Insomnia symptoms (Insomnia Severity Index (ISI) score > 10 ; moderate insomnia).

5.3 Exclusion criteria

For a participant to be eligible, all exclusion criteria must be answered "no":

- Pregnancy or lactation (Pregnancy is screened for through self-reporting as no risks regarding pregnancy have been identified for the described study procedures).
- Does not have daily access to smartphone/tablet
- Night shift during the time of the CBT-I treatment.
- Currently receiving pharmacological treatment for insomnia (e.g. benzodiazepines, hypnotics etc.).
- Severe psychiatric/somatic illnesses of relevance of their sleep (reported by participant).
- Diagnosed sleep disorders (e.g., OSA, narcolepsy).
- Does not have E-boks.
- Known abuse of alcohol or other substances.
- Suicide and self-harm thoughts (reported by participant).
- People judged incapable, by the investigator, of understanding the participant instruction or who are not capable of carrying through the investigation.
- For the EEG subgroup only (60 patients):
 - Age ≥ 65 years
 - Anatomy of the outer ear making it impossible to do ear EEG monitoring.
 - Ear piercings that are not compatible with ear EEG.
 - Previous stroke or cerebral haemorrhage and any other structural cerebral disease.
 - Teeth grinding (bruxism).
 - Allergic contact dermatitis caused by metals or generally prone to skin irritation.

5.4 Selection and screening of participants

Based on the 2021 National Health Profile more than 950.000 people suffer from chronic pain in Denmark [61] and it is the most common reason to visit the general practitioner [62]. Therefore, we will use a recruitment strategy with advertisements and social media campaigns. We have previously used this method with success for recruitment of chronic pain patients in other trials

[63]. Participants that respond to advertisements will after their initial phone contact, if they fulfill the initial eligibility criteria, receive written information material about the trial using E-boks, which is a digital system used for all communication between Danish authorities and citizens, and be invited to oral information about the study, possibility to ask questions and an eligibility examination at the Pain Center at Odense University Hospital (visit 1). Participants fulfilling all eligibility criteria and signing informed consent will be invited to an additional visit (visit 2 – Pain Center, Odense University Hospital). The final decision on inclusion of patients will be made at visit 2, followed by baseline testing and randomization.

5.5 Procedures of withdrawal and discontinuation criteria

A participant will be withdrawn from treatment:

- 1) In case of an unexpected serious adverse response (SAR). Participants will be instructed to cease the treatment immediately if a SAR is suspected. Follow-up is made regularly until the symptoms are resolved or stable.
- 2) If the participant during the trials wants to cease the treatment, the participant is withdrawn from the study treatment.
- 3) If the participant during the trial wants to withdraw from the study, the participant is withdrawn from the study and will not be contacted for further assessments.

All participants that are withdrawn from the study will be encouraged to complete all visits as scheduled. Participants that are withdrawn from the treatment will not be replaced and will be included in the intention-to-treat population. According to our sample size calculation, we will include participants enough to tolerate a drop-out rate of up to 30%. Both intention-to-treat and per protocol analysis will be performed and compared to assess the robustness of the primary analysis.

6. Statistical considerations and data reporting

6.1 Sample size estimation

Minimal clinical important difference for pain intensity is 15% [64] corresponding to a change of 1.0 points in this population [49]. With a SD for change of 2.0 for patients with chronic pain and insomnia [49], power of 80%, an alpha value of 0.05, a minimum of 63 participants in each group is required. With an expected drop-out of 30% [65] we plan to recruit 160 participants (80 for each group). Stopping rule: in the event that 130 patients have completed the 9 weeks follow-up before 160 patients have been recruited we will stop recruitment of further participants.

6.2 Statistical methods

Difference in change from baseline to 9 weeks in the two primary outcomes (ISI score or mean NRS pain in last 7 days, both being continuous variables) between the digital CBT-I group and the sleep hygiene education group will be estimated using a mixed linear model approach with ISI and NRS pain as outcomes, time (4 and 9 weeks or 1, 2, 3, 4, 5, 6, 7, 8 and 9 weeks, respectively), treatment arm (digital CBT-I or 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 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 digital CBT-I arm, i.e. a positive number expresses a favoring of the intervention. The pre-specified effectiveness analyses will be based on the intention-to-treat (ITT) principle, which includes all participants that are assessed and randomized at baseline. 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.

In assessing statistical significance, we will apply a sequential test procedure investigating the effect on ISI severity in the first step and the effect on pain intensity in the second step. This means that statistical significance in the second step will only be assessed if statistical significance has been reached in the first step. The significance level is set to 5%.

With respect to potential non-compliance, a per-protocol analysis will also be performed, with a per-protocol population defined as patients with an adherence to the treatment of at least 75%.

In responder analysis, a responder is defined as a patient who report a more than 30% and 50% decrease in insomnia and pain after 9 weeks. Treatment differences will be expressed by adjusted odds ratios. These will be based on a logistic regression model with treatment, baseline value of pain intensity and insomnia severity, and sex as covariates.

A detailed statistical analysis plan (SAP) will be made publicly available before the statistical analysis is initiated.

6.3 Trial interpretation

A 95% confidence interval excluding 0 or less points in pain intensity is interpreted as a demonstration of a clinical meaningful difference between the digital CBT-I and sleep hygiene education group. A 95% confidence interval excluding 1 or more points in pain intensity is interpreted as a demonstration of no clinical meaningful difference between the digital CBT-I and sleep hygiene education group. A complete guide to trial interpretation with respect to pain intensity is shown in Table 3.

Table 3: Trial interpretations

Scenario	Estimate	Lower bound CI	Upper Bound CI	
1.	≥ 1	≥ 1		We have demonstrated an intervention effect of clinically relevant magnitude
2.	≥ 1	$\geq 0, \leq 1$		We have demonstrated an intervention effect and obtained a positive intervention effect estimate of clinically relevant magnitude.
3.	≥ 1	≤ 0		We obtained a positive intervention effect estimate of clinically relevant magnitude, but we could not demonstrate an intervention effect
4.	$\geq 0, \leq 1$	≥ 0	≥ 1	We have demonstrated an intervention effect and obtained a positive intervention effect estimate.
5.	$\geq 0, \leq 1$	≥ 0	≤ 1	We have demonstrated an intervention effect but also the absence of an intervention effect of clinically relevant magnitude.
6.	$\geq 0, \leq 1$	≤ 0	≥ 1	We obtained a positive intervention effect estimate, but we could

				not demonstrate an intervention effect
7	$\geq 0, \leq 1$	≤ 0	≤ 1	We obtained a positive effect estimate but also demonstrated the absence of an intervention effect of clinically relevant magnitude.
8.	≤ 0		≥ 1	We obtained a negative intervention effect estimate, but we could not exclude that the intervention effect is of clinically relevant magnitude.
9.	≤ 0		$\geq 0, \leq 1$	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

The same principle is applied to the insomnia severity with a difference of 5 points instead of 1 point to define a clinically meaningful magnitude. The trial interpretation outlined in Table 3 with respect to pain intensity will be adapted in case we fail to demonstrate statistical significance with respect to an impact on insomnia severity.

7. Study safety

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

7.1 Adverse device (ear EEG research solution) effect

An adverse device effect (ADE) is defined as an adverse effect related to the use of the medical research solution.

Unexpected serious adverse device effect: A serious adverse device effect (USADE) is defined as an adverse effect that results in any of the following:

- Death
- A life-threatening illness or injury
- In-patient hospitalization or prolongation of existing hospitalization
- A permanent impairment of a body structure or body function
- Medical or surgical intervention to prevent life threatening illness
- Fetal distress, fetal death or congenital abnormality/birth defect

Unexpected serious adverse device effect - near incident: Serious adverse device effects also include situations in which the incidents mentioned in the previous definition could have occurred if suitable action had not been taken or if circumstances had been less fortunate.

7.2 Assessment of ADE and USADE

Assessment of intensity: In collaboration with a medical doctor, the investigator will assess the intensity of each ADE and this will be recorded in the eCRF using the following categories:

- Mild - an event that is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities
- Moderate - an event that is sufficiently discomforting to interfere with normal everyday activities
- Severe - an event that prevents normal everyday activities

Assessment of relationship to the device or procedures

- Causal – Relationship to device or procedures beyond reasonable doubt
- Probable – Relationship seems relevant and/or the event cannot reasonably be explained by another cause
- Possible – A causal relationship is weak but cannot be ruled out
- Unlikely – The event is most likely related to etiology other than the device or procedures
- Not related – Relationship can be excluded

7.3 Device deficiency

Device deficiencies are defined as insufficiencies or inadequacies in instructions for use, the deployment, the installation, the operation, or any malfunction of the research solution. This also includes any event that is a result of a use error or intentional misuse of the device.

7.4 Collection, recording and reporting of adverse device effects

All events meeting the definition of an ADE will be collected and assessed. During each contact with the site (site visit or telephone contact) the participant will be asked about ADE as well as device deficiencies.

All ADEs, either observed by the investigator or reported by the participant, will be recorded by the investigator on eCRF form and evaluated. The investigator must assess the involvement of the used device in the ADE. For any device deficiency, the research solution manufacturer (T&W Engineering A/S, (Martin Christian Hemmsen; phone: +45 51965195) may request the investigator to return the device (when possible) for investigation at the manufacturer's laboratories. In case of any USADEs, the manufacturer will be contacted. The primary investigator will report to the Danish Medicines Agency according to the national regulations:

- Any USADE
- Any device deficiencies that might have led to a USADE if:

- a) suitable action had not been taken or
- b) intervention had not been made or
- c) if circumstances had been less fortunate

For the purpose of this guidance and based on the definitions above, the following events are considered reportable events in accordance with MDR Art. 80(2): a) any serious adverse event that has a causal relationship with the investigational device or the investigation procedure or where such causal relationship is reasonably possible; b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; c) any new findings in relation to any event referred to in points a) and b). All reportable events will be reported to the ethics committee immediately, but not later than 2 calendar days after awareness by sponsor.

7.5 Follow-up of adverse device effects

During and following a participant's participation in the study, the investigator will ensure that adequate medical care is provided for any participants for any ADE.

All ADEs (including non-serious) must be followed up until the outcome of the event is "recovered", "recovered with sequelae" or "fatal", and until all events have been resolved. Cases can be closed with the outcome "recovering" when the participant has completed the study and is expected by the investigator to recover.

7.6 Monitoring plan

The study will be registered at ClinicalTrials.gov. This study will not have a formal data monitoring committee, and no trial audit is planned as this trial does not investigate drugs and the data collected by the ear-EEG research solution in this study is not used for assessment of performance and safety or CE marking of the device.

8. Funding and economy

8.1 Conflict of interest and financial support

The study is initiated by Prof. Henrik Bjarke Vægter, Prof. Jonas Bloch Thorlund, Prof. Bobby Zachariae and Prof. Preben Kidmose. T&W Engineering is the manufacturer of the research solution and will help in the development of investigator brochure and provide device and system services throughout the study period, including ongoing firmware updates to ensure data quality. The study is fully funded by grants from Sygesikringen 'danmark' (Health Insurance Denmark) and The Region of Southern Denmark. The funders have no role in the design, conduct or dissemination of the study.

8.2 Remuneration of the study participants

Patients that reside more than 25 kilometers away from the place of the study, will receive compensation for expenses for transportation following the applicable guidelines at the time of participation.

9. Collaboration

This investigation is based on the collaboration of three main parties: Department of Anesthesiology and Intensive Care Medicine, Odense University Hospital, University of Southern Denmark,

and Aarhus University (Department of Psychology and Behavioral Science and the Department of Electrical and Computer Engineering). T&W Engineering is the manufacturer of the ear-EEG research solution. Recruitment of participants and data collection are conducted by Department of Anesthesiology and Intensive Care Medicine. The collaborators from Aarhus University will perform EEG data analysis. Aarhus University are collaborators because of their important knowledge of digital CBT-I (Department of Psychology and Behavioral Science) and the ear-EEG research solution and machine learning expertise for sleep stage classification (the Department of Electrical and Computer Engineering). T&W Engineering will be involved in the ear-EEG data and data from the debriefing interview data about ease of use and comfort of the research solution.

9.1 Financial aspect of collaboration

Aarhus University (the Department of Electrical and Computer Engineering) will receive 334.000 DKK from the grant from Sygesikringen “danmark” to cover their expenses associated with analyses of ear-EEG data. Of these, T&W Engineering A/S will receive 125.000,- DKK to cover their expenses associated with delivery and support of 10 ear-EEG solutions in this study.

10. Ethics

The study will be conducted according to the declaration of Helsinki, approved by the Danish National Center for Ethics and data processing in connection with the study will be reported to the region of Southern Denmark’s list of on-going research projects via the Executive Secretariat at Odense University Hospital and Aarhus University’s record of research projects (for ear-EEG data). Only information relevant for the study will be collected. Data will be handled in accordance with the General Data Protection Regulation (GDPR) and the Data Protection Act.

10.1 The participants benefit and risks

The participants will potentially benefit from participating in the study with pain relief and improved sleep, and will gain knowledge and information about their sleep. Sleep deprivation is a serious problem for many people with chronic pain and it is believed that the improved treatment and knowledge about sleep in patients with chronic pain outweighs the potential risks in the current study. A risk analysis according to ISO 14971:2012 “Application of risk management to medical devices” has been conducted. Risks have been minimized or eliminated through appropriate design control. The risks associated with participated in the study are listed in Table 4. For more

information about the risk assessment for the ear-EEG research solution, please refer to the attached investigator's brochure.

Table 4: Risks and risk management

Event	Strategy
Allergic reaction to earbuds	The earbuds are removed immediately, and the affected area of skin is cleaned with water. All materials in contact with the skin are biocompatible, to minimize the risk of this event.
Soreness or skin irritation from prolonged wear	Sore skin (interfering with sleep) can be immediately alleviated by removing the earbud.
Earbud may break inside ear	In most cases it will be possible for the wearer to remove the damaged earbud themselves. If not, it is possible to have an audiologist do this, without significant risks or long-term effects.

10.2 Participant insurance

Participating patients are covered by the governmental patient insurance, which includes all patients in the Danish health care system.

10.3 Information to study participants and informed consent and letter of authority

Study participants will be recruited by advertising (see Appendix 8) by posting on site, universities, social media or webpages such as www.forsogsperson.dk.

The study information sheet (see Appendix 9) including the brochure "*Dine rettigheder som forsøgsperson i forsøg med medicinsk udstyr*" will be dispensed ahead of verbal study information meeting. The verbal information meeting will be arranged, so that thorough information is possible. Participants will be encouraged to bring a friend or family member. At the information meeting, the study procedure will be explained in detail under undisturbed conditions, i.e. the meeting will take place in a separate room and the informant will have no other planned tasks, no on call duties. Prior

to any study related activity, the principal investigator will give the participant oral and written information about the study in a form that the participants can read and understand. The principal investigator is responsible for ensuring that no participants is exposed to any study related examination or activity before the participant has given his/her written informed consent (see Appendix 10). The participant has the right to think for 24 hours before making his/her final decision about participation in the study. The written informed consent will be signed and dated by the person who seeks the consent and by the seeker. Informed consent forms and letters of authority will be kept and archived in the investigator file for at least 10 years. All study related procedures, included obtaining information about health, will be performed by a qualified person (study nurse) and all medical questions will be directed to a medical doctor on site.

10.4 Changes to clinical investigation plan or related procedures

Any substantial design changes of the device, amendments to the clinical investigation plan, the informed consent, or other written information provided to participants, and/or study procedures directly will be approved in writing by the ethics committee. No changes in the study procedures will be implemented without mutual agreement of the principal investigator and the collaborators. No substantial changes to the clinical investigational plan can be implemented before approval/favorable opinion unless necessary to eliminate immediate hazards to the participants.

10.5 Deviations from clinical investigation plan

Deviation to the clinical investigation plan will be avoided.

If deviations occur, the principal investigator will inform the collaborators who are responsible for analyzing and assessing the implication of the deviation. Any deviation from the clinical investigation plan will be documented stating the explanation for the deviation, the date and any actions taken.

The documentation for the deviations will be kept in the eCRF.

Significant deviations compromising or potentially compromising the safety of the participants, enrolment of non-eligible participants or any deviation, which significantly compromises the outcome of the study, must be reported to the ethics committee within the appropriate timelines indicated by the ethics committee.

10.6 Reporting of results

The main findings of the study, positive as well as negative and in-conclusive will be published in a publicly available database (e.g. www.clinicaltrials.gov). The main findings will furthermore be submitted for publication in peer reviewed journals.

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