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Protocol for a multi-center randomized controlled trial of digital cognitive behavior therapy for insomnia compared with digital patient education about insomnia in individuals referred to secondary mental health services in Norway.

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Title: *Protocol for a multi-center randomized controlled trial of digital cognitive behavior therapy for insomnia compared with digital patient education about insomnia in individuals referred to secondary mental health services in Norway.*

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Abstract

Introduction: Insomnia is highly prevalent in outpatients receiving treatment for mental disorders. Cognitive Behavioural Therapy for Insomnia (CBT-I) is a recommended first-line intervention. However, access is limited and most patients with insomnia who are receiving mental health care services are treated using medication. This multi-centre randomized controlled trial (RCT) examines additional benefits of a digital adaptation of CBT-I (dCBT-I), compared with an online control intervention of Patient Education about insomnia (PE), in individuals referred to secondary mental health clinics.

Methods and analysis: A parallel group, superiority, RCT with a target sample of 800 participants recruited from treatment waiting lists at Norwegian psychiatric services. Individuals awaiting treatment will receive an invitation to the RCT, with potential participants undertaking online screening and consent procedures. Eligible outpatients will be randomized to dCBT-I or PE in a 1:1 ratio. Assessments will be performed at baseline, 9-weeks after completion of baseline assessments (post intervention assessment), 33-weeks after baseline (6 months after the post intervention assessment) and 61-weeks after baseline (12 months after the post intervention assessment). The primary outcome is between-group difference in insomnia severity 9-weeks after baseline. Secondary outcomes include between-group differences in levels of psychopathology, and measures of health and functioning 9-weeks after baseline. Additionally, we will test between-group differences 6 and 12 months follow-up, and examine any negative effects of the intervention, any changes in mental health resource use, and/or in functioning and prescription of medications across the duration of the study. Other exploratory analyses are planned.

Ethics and Dissemination: The study protocol has been approved by the Regional Committee for Medical and Health Research Ethics in Norway (Ref: 125068). Findings from the RCT will be disseminated via peer-reviewed publications, conference presentations and advocacy and stakeholder groups. Exploratory analyses, including potential mediators and moderators, will be reported separately from main outcomes.

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Strengths and limitations

- Use of an automated intervention in individuals awaiting assessment for face-to-face treatment for mental disorders could yield important information about how to stratify treatment interventions and offer insights into the role of sleep patterns in mental disorders.
- A large-scale multicentre trial, with broad eligibility criteria, undertaken in a public sector service increases the likelihood that findings are generalizable to other clinical settings.
- Sample size allows for detection of medium-small effect sizes on secondary outcomes.
- Limitations include potential sampling biases e.g. recruitment via self-ratings of insomnia rather than clinical evaluation.
- The sample comprises non-urgent referrals to mental health services, so translation of the findings to acutely ill psychiatric populations may be limited.

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Background

Insomnia is characterized by subjectively reduced sleep quality, in the form of delayed sleep onset or frequent or prolonged awakenings at night, and is associated with reduced daytime functioning.[1 2] It is highly prevalent in individuals with mental disorders.[3] In a study of more than 2000 secondary psychiatric outpatient clinic attendees in Norway, about 70% reported a concurrent sleep disturbance regardless of primary diagnosis; and 40% reported severe sleep difficulties.[4] Traditionally, insomnia has been regarded as a secondary problem that often arises among those experiencing a primary mental disorder. Recently, this view has been challenged, and the current edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) now advises clinicians to record "Insomnia Disorder" as an independent comorbidity (rather than a secondary diagnosis).[1] This change is important for clinical practice as it has increased the prominence of insomnia as a separate condition in psychiatric populations and draws attention to the sub-optimal outcomes of standard psychiatric treatments in individuals with co-occurring insomnia[5 6]. Further, it is increasingly clear that even when insomnia symptoms are a core symptom of the presenting syndrome, they may be more treatment refractory than other phenomena with 40%-70% of individuals who show improvement with antidepressants treatments continuing to report ongoing sleep difficulties.[7-11] Overall, clinicians and researchers now acknowledge the reciprocal relationship between sleep and mental disorders, such that they often perpetuate and exacerbate each other. This has raised awareness of the need to target interventions for insomnia, rather than assuming that it will simply be resolved following general psychiatric treatment.

While medications are employed for insomnia, there is reluctance to co-prescribe these medications with the complex regimes that are routinely used to treat mental disorders. Concerns range from their addictive potential, the risk of drug interactions especially with polypharmacy, and their low level of medium-to-long term effectiveness.[12] As such, there is a growing interest in the application of psychological interventions for insomnia, such as Cognitive Behavioural Therapy for Insomnia (CBT-I) which has a more favourable risk-to-benefit ratio and is a recommended first-line treatment for insomnia.[13 14] Further, several review articles and meta-analyses that synthesize data from randomized controlled trials (RCT) demonstrate that this intervention may also be effective in reducing sleep problems in individuals with comorbid physical and/or mental disorders.[15-19]

Taken together, it is clear that trials of CBT-I would be a useful addition to the knowledgebase regarding sleep and mental disorders. However, there is a paucity of trained CBT-I therapists and insufficient numbers of expert practitioners are available within specialist mental health services. This

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undermines the feasibility and utility of conducting large-scale RCTs relying on face-to-face therapy as it would be difficult to translate the findings to day-to-day practice. Self-guided, fully automated, digital CBT-I (dCBT-I) has been developed, tested and employed as a means of increasing access to the intervention to large, geographically spread populations. Automated dCBT-I has previously been shown to reduce insomnia severity among individuals with comorbid mental disorders in non-clinical populations,[20] to reduce depressive symptoms in individuals with sub-clinical depressive presentations,[21] - and across different sociodemographic groups.[22] Also, it appears to reduce psychotic symptoms in non-clinical samples.[23] These findings are encouraging and indicate that self-guided dCBT-I could be beneficial even in secondary care settings, such as mental health care outpatient clinics. One small trial in older men who were receiving psychiatric treatment for depression found that automated dCBT-I was effective in reducing insomnia severity 9 weeks after baseline assessment, and suggests a larger, longer-term trial is warranted.[24] Importantly, automated dCBT-I could be initiated immediately after an intake assessment (even if the individual is awaiting other interventions) and this strategy could potentially reduce the overall duration or intensity of specialist care.

Aims

The protocol outlines a two-arm, parallel-group, superiority RCT that examines the additional benefits of dCBT-I compared with a control intervention of digital patient education about insomnia (PE) offered over 9 weeks. This multi-centre RCT will recruit adults who have been referred to public sector secondary psychiatric outpatient clinics in Norway who are awaiting treatment of a mental disorder.

The overarching aim of the trial is to test the effectiveness of dCBT-I in a clinical, trans-diagnostic population of non-urgent referrals to adult psychiatric outpatient services. The primary endpoint is outcomes 9-weeks after the baseline assessment. This endpoint was selected because it allows sufficient time to complete the intervention, and the average wait-time before routine treatments commence is currently estimated at about 12 weeks, i.e. few patients will have initiated regular treatment by 9 weeks, allowing sufficient time for most participants to complete the key phase of the RCT prior to exposure to any specific psychiatric interventions that are proposed for the presenting condition. We will also assess outcomes 33- and 61-weeks after baseline assessments to test if there are any long-term gains or adverse effects associated with the experimental intervention.

The trial is designed to address the following hypotheses: Compared with PE, the dCBT-I intervention will, at each follow-up point (9-, 33- and 61-weeks after baseline assessment), be associated with:

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1) lower severity of self-reported symptoms of insomnia (primary outcome).
2) lower levels of self-reported psychopathology and somatic symptoms.
3) improved health and cognitive function.
4) less health resource utilization (operationalized as the number of treatment sessions received during the 12-month trial),
5) lower prescriptions rates for hypnotic, sedative/anxiolytic, and anti-depressant medications.

Secondary aims include analyses to test if there are specific subgroups that are more likely to benefit from dCBT-I; if exposure to dCBT-I or PE is associated with increased or reduced willingness to participate in face-to-face interventions for mental disorders in the future (e.g. individual treatment delivered by a therapist at a clinic or via telemedicine (if offered during COVID safety protocols are remain in place)); whether dCBT-I is associated with any negative effects; and/or whether dCBT-I is associated with any additional reduction in sick-leave, improved work productivity and daily activities outside of work.

Exploratory and additional analyses: We will perform mediation analyses, and plan to undertake cost-benefit analysis; longer term health and social outcomes (>12 month) will be assessed from objective data available via national registries. Also, participants recruited at the lead centre (St. Olavs Hospital, Trondheim) will be invited to participate in an actigraphy study examining objective recordings of sleep before, during, and after the intervention (target sample ~40).

Methods and analysis

The protocol for the RCT follows the SPIRIT guidelines (Standard Protocol Items for Randomized Trials)[25] and Figure 1 shows the flow chart for the recruitment and assessments. A completed SPIRIT checklist has been uploaded and a completed World Health Organization Trial Registration Data Set can be found in supplementary file 1.

Trial design

A multi-centre, parallel-group, superiority RCT of individuals who meet established criteria for clinically significant insomnia according to self-report assessments undertaken with the internationally-recognized standard rating. Trial participants will be randomized 1:1 to either dCBT-I or PE.

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Recruitment

Recruitment will be undertaken at psychiatric outpatient clinics located in public health care organizations ('health care trusts') across rural and urban areas in Norway. Individuals referred for assessment for outpatient treatment of a mental disorder at the participating clinics will be sent an invitation to join the RCT. The invitation will be sent when the patient is registered on the waiting list for commencing mental health treatment (also see the supplementary file 2 for additional details). This means that screening and randomization can be completed, and digital interventions commenced before the individual attends their first scheduled treatment session.

Eligibility

Individuals with an interest in participating will be directed to a website that provides information about the RCT. They will then be offered the opportunity to participate in the consent procedure and complete an online screening assessment for eligibility. Individuals who give written informed consent and meet trial inclusion criteria will receive a telephone call from an investigator who will answer any questions, ensure that potential participants received all the relevant written documentation about the RCT, and provide technical support regarding the digital intervention.

Inclusion criteria:

1. Individuals aged >= 18 years
2. Willing and able to provide written informed consent.
3. Insomnia Severity Index (ISI) > 11; (this cut-off score is employed as we have previously used it to identify individuals experiencing clinically significant insomnia and/or those who may benefit from dCBT-I[26]; also, it is the most sensitive to detect a diagnosis of Insomnia Disorder in a Norwegian sample[27]).

Exclusion criteria:

1. Sleep apnea screening: An Epworth Sleepiness Scale score >=13, indicative of high levels of objective daytime sleepiness associated with organic sleep disorders[28] and/or positive endorsement of a screening question for sleep apnoea (this asks if they "usually or everyday snore and stop breathing").
2. Medical history contra-indicating use of CBT-I, e.g. (i) epilepsy plus self-report of >=1 seizure

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within the preceding 12 months, or (ii) recent cardiac surgery, or (iii) currently in an attack phase of multiple sclerosis.

3. Individuals whose work schedule includes night shifts.
4. Pregnancy
5. Inadequate opportunity to sleep or living circumstances that prevent modification of sleep pattern (e.g. having an infant residing home).
6. Currently receiving psychological treatment for insomnia.
7. Not registered at or under the care of any of the trial centres.

Interventions

Digital CBT-I: CBT-I[29] is a multicomponent intervention that includes the following: psychoeducation about sleep, sleep hygiene, sleep restriction therapy, stimulus control and challenging dysfunctional beliefs and perceptions about sleep. This trial employs a digital CBT-I program named Sleep Healthy Using The internet (SHUTi),[20 30] which has been translated into Norwegian and employed in our previous RCTs.[31] SHUTi is fully automated and requires no contact with health care personnel and can be accessed on computers or hand-held devices using a browser-based interface. The program is interactive and comprises the same elements included in face-to-face CBT-I[29] (including tailoring of the program to individual needs). The user is provided with access to new educational, behavioral or cognitive modules in the week after completing a previous module. Between modules, users enter self-monitoring information into a digital sleep diary.

Digital patient education about insomnia (PE): The PE offers digital sleep hygiene information that can be accessed on computers or hand-held devices and has been used in multiple RCTs of SHUTi for insomnia.[20 26 30 31] There is some content overlap with that included in the dCBT-I intervention, but it does not include any of the interactive features of the dCBT-I intervention and all the information is available to the user from the outset.

Randomization

This RCT employs the same randomization procedure as in a previous Norwegian trial of dCBT-I.[26] The automated procedure involves block randomization with varying block sizes and cannot be influenced in any way by the researchers. Participants are blinded to their group allocation, but complete blinding is not possible as the participants may be able to discern whether they have received the active or control condition.

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Withdrawal

Participants will be informed that they can withdraw from the trial at any time, without stating any reason and without any consequences whatsoever for their mental health treatment.

Crisis management procedure

All clinics have an emergency psychiatric service (24/7) for patients who require immediate assistance, experience crises, distressing increases in symptoms and/or marked deteriorations in functioning. This service is responsible for all clinic attendees, including trial participants. If any trial participant utilizes the emergency service, the investigators will be informed and a decision made regarding continuation in the RCT and/or whether the crisis constitutes a trial-related adverse event.

Outcome assessments

The trial will adhere to the recommended standards for the research assessment of insomnia.[32] Self-report questionnaires will be completed online at baseline, post assessment (9 weeks after baseline), 6 months after the post assessment (33 weeks after baseline) and 12 months after the post assessment (61 weeks after baseline). Table 1 summarizes the type and timing of all assessments (also see the supplementary file 3 for additional details). Individuals will receive an automated message prompting them to complete the relevant online assessments at each time point

Demography and Clinical Characteristics

As shown in Table 1, key demographic information will be recorded at baseline.

Self-reported clinical history will include information about sleep problems, medication use, previous medical, mental, and physical disorders, treatments, and admissions. Data will also be collected regarding type and number of physical disorders (from a list of 20 common medical conditions) and mental disorders (from a list of 9 common mental disorders).

Sleep measures:

Primary outcome measure:

The Insomnia Severity Index[33] is a 7-item questionnaire assessing the severity of insomnia symptoms the last 14 days.

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Secondary outcome measures:

Other measures of sleep and chronotype:

The Consensus Sleep Dairy[34] assesses prospective daily sleep-wake patterns on at least 10 of 14 consecutive days.

The Reduced Morningness – Eveningness Questionnaire[35] measures chronotype i.e. time preference for daily activities, including bed-times.

Bergen Insomnia Scale[36] assesses symptoms of insomnia based on the insomnia criteria in the DSM-IV.[37]

Level of psychopathology & functional impairment:

The Outcome Questionnaire – 45.2[38] assesses mental health status, including symptom distress, interpersonal relations, and social role functioning.

The Hospital Anxiety and Depression Scale[39] assesses non-vegetative symptoms of anxiety and depression.

Nightmares and nocturnal mentation:

Selected items from the *Nightmare Frequency Questionnaire*[40], *Nightmare intensity*[41] and *Nocturnal mentation*[42] questionnaires will be used to assess frequency and intensity of nightmares and nocturnal mentation.

Measures of somatic symptoms and health

The Chalder Fatigue Scale[43] assesses levels of daytime physical and psychological fatigue.

Euroqol-5D[44] assesses general health state and allows measurement of Quality Adjusted Life Years in individuals presenting with a range of physical and mental disorders.

Alcohol Use Disorders Identification Test – Consumption assesses the frequency and amount of alcohol use.

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Headache Impact Test – 6[45] assesses the intensity and consequences of headaches the last month.

Work performance:

Work Productivity and Impairment Questionnaire General Health[46] assesses work performance and impairment in daily living.

Cognitive function

The Cognitive Complaints in Bipolar Disorder Rating Assessment assesses subjective cognitive function.

Intervention-Related Assessments

Expectations: one item assessing to what extent the patient thinks a digital sleep intervention can work for them (1= not at all, 9 = perfectly).

Self-efficacy: At baseline, a questionnaire assessing self-efficacy related to making behavioural changes.

The Negative Effects Questionnaire (NEQ)[47] assesses negative effects of digital interventions.

Impact on future treatment: two items assesses if exposure to digital interventions has impacted on willingness to participate in face-to-face therapy for mental disorders, and/or sleep problems.

The Use of Sleep Strategies assesses how often individuals use different therapeutic techniques for sleep and their perception of its utility.

Resource use and national registries

Using objective data available from national registries we will collate information on participants to allow to explore group differences before and/or after randomization-

a) reasons for referral;

b) diagnoses;

c) substance use, person injury, incident leading to any hospital admission;

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d) appointments, treatments and admissions at mental health care clinics;

e) dose, timing and type of prescribed medications and changes recorded during the RCT;

e) costs of treatment offered by the public services;

f) sick leave or in receipt of disability benefits;

g) if any deaths occur during the course of the study, we will record the cause (as recorded on the death certificate).

Subgroup data collection of objective sleep and circadian assessments

About 40 participants recruited at St Olavs Hospital will be invited to undertake concurrent actigraphy monitoring of sleep-wake patterns.[48]

Sample size

The primary outcome is difference in ISI scores at 9 weeks post-baseline. Published RCTs of CBT-I or dCBT-I report an effect size (ES) (Cohen's d) between 0.8-2.0 for these interventions compared with control conditions for community samples or clinical trials in populations with insomnia. However, we anticipate digital interventions may not have such a large effect in a trans-diagnostic psychiatric outpatient population,[24] so we have estimated the RCT sample size based on a Cohen's $d = 0.5$. Additionally, we wanted the sample size to provide adequate statistical power to detect small to moderate ES (Cohen's $d = 0.3$ to 0.5) on the secondary outcomes (levels of psychopathology, etc). Lastly, other RCTs of CBT-I report sample attrition rates of between 12% and 50%.[20 21] As the planned RCT involves limited contact between investigators and participants and has a 12-month follow-up, we have assumed a study dropout rate of about 50%. Therefore, we aim to recruit 800 participants, to enable us to retain 400 patients (200 in each treatment arm) at the end of the RCT. For a two-sample t-test with alpha=0.05, this sample size gives a power of 99.9%, 93.7%, and 84.9% of detecting a difference of Cohen's $d = 0.50$, 0.40, and 0.30, respectively.

We did not undertake any statistical power calculations related to the analysis of service utilization, medication use etc., as assessed in the National Registers, or cost-benefit analysis. Missing data is unlikely to be an issue when examining the National Registers.

Statistical analytic plan

Descriptive statistics. Summary descriptions of demographic and clinical characteristics will be presented for each group. Categorical and binary variables will be presented as counts and percentages,

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continuous variables will be presented as means and standard deviations or medians and interquartile ranges, as appropriate.

Analysis of primary and secondary outcomes. The key outputs will be intention to treat analyses, i.e. everyone who is randomized will be analyzed. Per-protocol analyses will be reported for individuals who complete >=4 dCBT-I modules. There will be no planned interim analyses during the inclusion period, though we will publish findings from self-reported data prior to the registry data.

We plan to use linear mixed model analysis to examine the difference between the two randomized groups on the primary and secondary outcomes with continuous variables. The model will include time, group, time-group interaction, and baseline covariates. For binary secondary outcomes, logistic mixed model analysis will be used. Linear mixed models (logistic mixed models) provide unbiased (approximately unbiased) results when the data are missing at random (MAR). Model assumptions will be reviewed and if the assumptions are not met, this will be handled using bootstrapping, logarithmic transformations, or analysed using non-parametric testing as appropriate. We will assess the influences of deviations from MAR in sensitivity analyses as described below.

Mediation and moderator analysis. In order to identify if changes in insomnia symptoms, levels of psychopathology, or cognitive function are important mediators of the effect of the digital treatment, we will perform mediation analyses assessing following the conceptual principles described by Kraemer et al.[49]

Sensitivity analysis. To investigate the influence of deviations from the MAR assumption, we will use a pattern-mixture models (PMMs) to simulate a range of situations where the data for both primary and selected secondary outcome variables are missing not at random (MNAR).

Ethics and dissemination

The RCT follows the guidance and principles outlined in the Revised Declaration of Geneva.[50] All eligible participants will be required to give online written informed consent before study entry. An copy is available upon request. Participants will be provided with written and printable information regarding the RCT, which will also be repeated in a telephone call with an investigator. Both the written and oral information emphasize that participation is voluntary, that individuals will receive the same standard of care and treatment at the mental health clinic regardless of their participation, that

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they may withdraw from the trial at any time without any consequences for their clinical care and that they do not need to give a reason for withdrawal.

Self-report data will be de-identified and stored in encrypted and password protected databases that are compliant with the General Data Protection Regulation (GDPR). Data from National Registries will be downloaded and incorporated into the files and anonymized.

The findings from the RCT will be disseminated via conference presentations and peer-reviewed scientific publications. The first academic publication will report any between-group differences on self-reported outcomes. Subsequent academic publications will report findings related to data extracted from the national registries, health economic analyses and mediation and moderation analyses. The main findings will also be presented to the patient user groups. The investigators will adhere to international guidelines regarding multi-authorship of manuscripts.

Patient and public involvement

The service user group for mental health care at the Central Norwegian Health Trust were consulted regarding the study outline and provided feedback on the aims of the trial and the assessments included in the protocol.

Study monitoring

A Data and Safety Monitoring Committee will meet weekly initially (during the start-up phase), and then monthly to oversee study progress, technical issues, status at the included sites and any reports of severe side effects. Other meetings can be convened if a specific problem or serious and untoward incident is reported. The committee comprises the project leader, project coordinator, and the investigators involved with overseeing recruitment and eligibility. Clinical representatives from participating health care hospital trusts, statistical advisors, administrative leaders, and other representatives will be co-opted as needed. The trial sponsor and the included health care trusts routinely and randomly audits one or more ongoing projects each year. The audit process ensures that trial protocols are followed, and ethical standards upheld. If any important protocol amendments are necessary, these will first be evaluated by the ethics committee and published on relevant study websites.

Discussion

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The utility of dCBT-I, and its impact on insomnia, psychopathology, cognitive functioning, and general health in routine clinical settings is not yet established. Given the bidirectional relationship between and sleep and mental disorders, interventions that are effective in reducing insomnia severity may also have benefits for comorbid psychiatric conditions.[51-53] For instance, one meta-analysis of CBT-I for insomnia in individuals with physical and mental disorders reported small to moderate effect sizes on comorbid symptoms with larger effects for psychiatric symptoms,[19] while another meta-analysis demonstrated small to medium ES for the effect of CBT-I on depressive symptoms.[54] It is possible that improvement in sleep early in the treatment process could lead to earlier response and/or improved outcomes of the presenting mental disorder. While findings of CBT-I research are encouraging, it is noteworthy that many RCTs do not have adequate statistical power to enable detection of effects on a broader range of symptoms and phenomena (beyond sleep), while others have been conducted in convenience or non-clinical samples. This means the effects of CBT-I on sleep in many mental health treatment settings are unclear. The current RCT aims to address some of these knowledge gaps, the sample size is calculated to allow detection of small-medium effect sizes on these secondary outcomes, and the trial is conducted in a trans-diagnostic clinical sample.

There are scientific limitations associated with conducting an RCT in heterogenous clinical samples attending different outpatient settings. First, diagnoses will be recorded by the clinicians at the clinics and not by the investigators, and there may be between-clinic differences in how some diagnoses are recorded. Also, there may be variability between clinics and between diagnostic subgroups regarding the waiting time for a first treatment session. Whilst most patients are likely to complete the course of dCBT-I before routine psychiatric outpatient treatment commences, others may experience an overlap between interventions. Thus, the trial may be a test of the effectiveness of dCBT-I when offered at an early stage of psychiatric treatment rather than prior to the introduction of routine care. Moreover, secondary psychiatric services, and health care policies are continuously evolving, and it is conceivable that outpatient assessment and treatment protocols might change after the RCT has begun. Finally, there are 20 outpatient clinics that have agreed to recruit participants to the trial, but most have not been able to do any piloting of the protocol (partly due to COVID, etc). We do not know how much recruitment will differ between urban and rural areas in Norway, and/or if additional clinics will need to be added (e.g. if recruitment is behind expected rates). This precludes using randomization sequences that are stratified according to clinic. Despite these limitations, we believe the results of this trial will be important in moving the field forwards in its understanding of the feasibility and utility of

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fully automated dCBT-I in clinical samples of psychiatric outpatients with a wide range of mental disorders, and how treatment of insomnia can affect other important clinical and social outcomes.

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Conflict of interest

Lee Ritterband report financial or business interests in BeHealth Solutions and Pear Therapeutics, two companies that develop and disseminate digital therapeutics (including by licensing the therapeutic developed) based in part on early versions of the software from the University of Virginia, which is used in the research reported in this Article. These companies had no role in preparing this manuscript. Dr. Ritterband is also a consultant to Mahana Therapeutics, a separate digital therapeutic ompany not affiliated with this research. The terms of these arrangements have been reviewed and approved by the University of Virginia in accordance with its policies. All other authors declare no competing interests.

Author statement

Study design was undertaken by the research team: HK, SBS, ØV, KL, GM, SL, MRS, SKD, BH, SGS, KH, TCS, AGH, LR, BS, and JS. HK conceived of the study and produced the first draft of the protocol paper with additional input form SBS, ØV, and JS. SL and MRS wrote the statistical analytic plan. All authors contributed to the drafting of the submitted version of the study protocol and all authors approved the final version of manuscript.

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Table 1: Key measures and timing of assessment

	Screening &/or Baseline	9-week follow-up	33-week follow-up	61- week follow-up
Demography & Clinical Characteristics				
Demographics (Age, Sex, Ethnicity)	X			
Marital status	X		X	X
Number of children living at home	X		X	X
Years of education	X			
Employment status	X	X	X	X
Medication use	X	X	X	X
Duration of sleep problems	X			
Previous treatments for mental disorders	X			
Previous treatments for insomnia	X			
Previous psychiatric hospital admissions	X			
Physical health	X			
Mental health	X			
Sleep and Circadian Rhythms*				
Insomnia Severity Index (ISI)	X	X	X	X
Brief Morningness Eveningness Questionnaire (rMEQ)	X		X	X
Consensus Sleep Diary	X	X	X	X
Bergen Insomnia Scale (BIS)	X	X	X	X
Epworth Sleepiness Scale (ESS)	X			
Level of psychopathology				
Outcome Questionnaire – 45.2 (OQ-45.2)	X	X	X	X
Hospital Anxiety & Depression Scale (HADS)	X	X	X	X
Nightmares and nocturnal mentation				
Nightmare Frequency Questionnaire (NFQ)	X	X	X	X
Nightmare intensity (CAPS)	X	X	X	X
Nocturnal mentation (DRFS)	X	X	X	X
Somatic symptoms and health				
Chalder Fatigue Questionnaire (CFQ)	X	X	X	X
EuroQol (EQ-5D)	X	X	X	X
Body Mass Index	X	X	X	X
Alcohol Use Identification Test - Consumption (AUDIT-C)	X	X	X	X
Headache Impact Test – 6 (HIT-6)	X	X	X	X
Cognitive function				
Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)	X	X	X	X
Intervention related assessments				
Treatment expectations	X			
Self-efficacy for sleep related behavioral change	X	X		
The Negative Effects Questionnaire (NEQ-20)		X		
Impact on future treatment		X		
Use of Sleep Strategies		X	X	X
Work Capacity & Resource Use (Registry data)				
Work Productivity and Impairment Scale (WPAI)	X	X	X	X
Health service utilization and ICD-10 diagnoses	X			X
Prescribed medications	X			X
Number of hospital admissions (and reasons)				X
Resource use				X
Cause of death				X

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*NB: Actigraphy data will be collected at each timepoint for sample recruited via St. Olavs University Hospital.

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Figure 1. Flow chart of timeline for a randomized controlled trial of digital interventions for insomnia.

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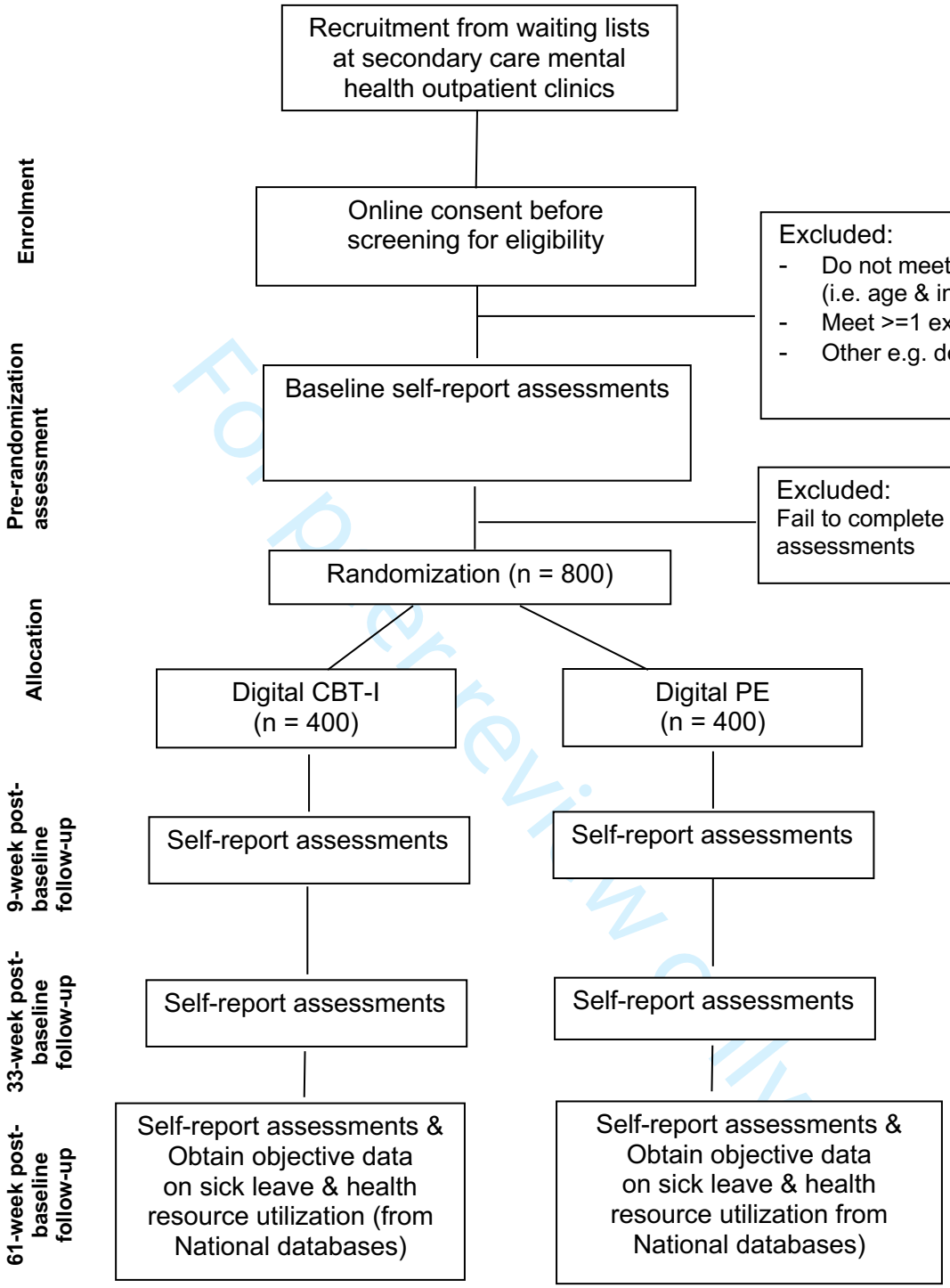

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SUPPLEMENT 1

Title: *Protocol for a multi-center randomized controlled trial of digital cognitive behavior therapy for insomnia compared with digital patient education about insomnia in individuals referred to secondary mental health services in Norway.*

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World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	CinicalTrials.gov: NCT04621643
Date of registration in primary registry	November 9, 2020
Secondary identifying numbers	Regional Committees for Medical and Health Research Ethics in South East Norway (125068).
Source(s) of monetary or material support	The Norwegian Research Council, grant number 273623
Primary sponsor	St. Olavs University Hospital (stolav.no)
Secondary sponsor(s)	None
Contact for public queries	HK (havard.kallestad@ntnu.no), SS (Simen.b.saksvik@ntnu.no), ØV (oystein.vedaa@ntnu.no)
Contact for scientific queries	HK (havard.kallestad@ntnu.no)
Public title	A digital intervention for insomnia for outpatients in mental health care.
Scientific title	A multi-center randomized controlled trial of digital cognitive behavior therapy for insomnia compared with digital patient education about insomnia in individuals referred to secondary mental health services in Norway.
Countries of recruitment	Norway
Health condition(s) or problem(s) studied	Mental Disorders, Insomnia
Intervention(s)	Active treatment: Digital Cognitive Behavior Therapy for Insomnia (Sleep Healthy Using The internet, SHUTi).
	Comparator: Digital patient education about insomnia
Key inclusion and exclusion criteria	Inclusion: Age >= 18 years old. Score on the Insomnia Severity Index >= 12. Willing and able to provide consent.
	Exclusion criteria: Individuals scoring >= 13 on the Epworth Sleepiness Scale (ESS), and/or answering that they usually or every day snore and stop breathing (i.e., they positively endorse pre-selected indicators of sleep apnoea); self-report of the presence of any medical conditions where a fully automated CBT-I may be contra-indicated (e.g. epilepsy, recent heart surgery); and/or participating in shift work; and/or pregnancy; and/or having inadequate opportunity to sleep; and/or currently receiving psychological treatment for insomnia, and/or not registered at or under the care of any of the trial centers
Study type	Interventional
	Allocation: Randomized intervention model. Parallel assignment model: Blind (subject)
	Primary purpose: Intervention
Date of first enrolment	December 2020
Target sample size	800
Recruitment status	Recruiting
Primary outcome(s)	The Insomnia Severity Index
Key secondary outcomes	Sleep Diaries, Mental health, Physical Health, Nocturnal mentation, Cognitive function, Diurnal preference, Work productivity, Sick leave, Medication use, Health resource use.

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SUPPLEMENT 2

Title: *Protocol for a multi-center randomized controlled trial of digital cognitive behavior therapy for insomnia compared with digital patient education about insomnia in individuals referred to secondary mental health services in Norway.*

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Recruitment

All individuals will be patients who have been referred to treatment for a mental disorder at one of the secondary outpatient clinics. As part of the standard routine in public mental health care outpatient clinics, these referrals, along with all other available patient information, are evaluated to establish if 1) the patient's mental health condition is severe enough to warrant treatment in secondary health care, of so 2) if it is an urgent or non-urgent case, i.e. if there is an acute suicide risk or other risk for severe deterioration of condition. In urgent cases, the patients are offered emergency treatment in mental health care. The non-urgent patients are placed on a waiting-list to receive treatment for their condition at the clinic and will be sent written information about this, their patient rights, and instructions for who to contact in case the patient experience a deterioration of the condition in the waiting period. This is sent to the patient and their General Practitioner by the clinic (by mail and/or electronically) immediately after the evaluation team have made their decision, usually the same day. This procedure follows the guidelines by the Norwegian Directorate of Health. In the written information the patients at the participating clinics will additionally receive information about this trial and a description of where to find the trial website. This means that non-urgent patients will be invited and screening and randomization can be completed and the digital interventions will have commenced before the individual attends their first formal clinical treatment session.

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SUPPLEMENT 3

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Outcome assessments

Sleep measures:

Primary outcome measure:

The Insomnia Severity Index (ISI)[31] is a 7-item questionnaire assessing the severity of insomnia symptoms the last 14 days. Each item is rated on a 0 to 4 rating scale with higher scores indicating more severe symptoms. The ISI has good psychometric properties and is validated for online use.[32] Range is 0-28 with higher values represent higher levels of insomnia symptom severity. A cut-off of 7 or below is used to indicate normal sleep and used to indicate remission after the interventions, and a reduction of 8 points during the interventions is used to indicate response to the intervention.[31]

Secondary outcome measures:

Other measures of sleep and chronotype:

Consensus Sleep Dairy: Prospective daily sleep-wake patterns will be assessed with the consensus sleep diary[33] which will be completed by the participant at baseline and each follow-up point for at least 10 out of 14 consecutive days. Individuals will be asked to record their bed-time, sleep onset latency, wake after sleep onset, number of nocturnal awakenings, time of final awakening in the morning, and rise-time, in addition sleep quality will be rated on a 5-point scale (with a higher score indicating better sleep quality).

Reduced (also known as Brief) Morningness – Eveningness Questionnaire (rMEQ): The rMEQ is a widely used measure of chronotype i.e. time preference for daily activities, including bedtimes. The rMEQ has five items yielding scores from 4 to 25, with lower scores indicating a preference for "eveningness" and higher scores indicating a preference for "morningness". Scores can be categorized as: definitely evening type (score <8), moderately evening type (score 8-11), neither type (score 12-17), moderately evening type (score 18-21), and definitely morning type (score >21).[34]

Bergen Insomnia Scale[35]*:* comprises six items that assesses symptoms of insomnia based on the insomnia criteria found in the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (American Psychiatric Association).[36]

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Level of psychopathology & functional impairment:

The Outcome Questionnaire – 45.2 (OQ-45.2) is a 45 item self-report scale assessing mental health status. The scale is specifically designed for assessing patient progress throughout therapy and is widely used clinically, and as an outcome measure in clinical trials. It has excellent internal consistency and is shown to be highly correlated with well-known outcomes such as the Symptom Checklist 90R, Beck Depression Inventory, The State Trait Anxiety Inventory, The inventory of interpersonal problems, The Social Adjustment Scale, and the SF-36.[37] The scale is scored on a scale of 0 (=never) to 5 (=almost always) giving a range of 0 to 180, with higher scores indicating higher levels of psychopathology. The OQ-45.2 has three validated subscales: symptom distress, interpersonal relations, and social role functioning (perceived level of difficulties in the workplace, school or home duties). Results will be reported for the sum score, and for the three subscales. The OQ-45.2 has an established clinical cut-off value and reliable change index.[37]

The Hospital Anxiety and Depression Scale (HADS)[38] is a 14-item questionnaire assessing non-vegetative symptoms of anxiety and depression on a 0 to 3 likert scale. The sum score can be used as a measure of general psychological distress and is widely used in the community, general practice and psychiatric settings. It has a range of 0 to 42 points with higher scores indicating higher levels of psychological distress.

Nightmares and nocturnal mentation:

The Nightmare Frequency Questionnaire (NFQ)[39]: One item from the NFQ assessing of frequency of nights with nightmares (in days per week, month or year).

Nightmare intensity[40]*:* One item from the clinical administered PTSD-scale (CAPS)[40] assessing the intensity of nightmares on a four point Likert-type scale ranging from 1 (= minimal) to 4 (=extreme).

Nocturnal mentation[41]*:* Three items from the Dream Recall Frequency Scale (DRFS) are used to assess nocturnal mentation and can be used as a proxy for REM sleep fragmentation.[41] The items are scored on a 0 (=never) to 8 (=almost every day/night) and assess how often the participant is aware of having thoughts during sleep, how often night-time thoughts affect mood next day, and how often the participant tells others about their night-time thoughts, giving a total score of 0 to 24.

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Measures of somatic symptoms and health

The Chalder Fatigue Scale (CFS)[42] is a 11-item questionnaire assessing levels of daytime physical and psychological fatigue on a 0 to 3 likert scale (0=less than usual, 3=much more than usual). The scale has a range of 0 to 33 with higher scores indicating higher levels of fatigue. Two additional items assess duration of fatigue (0=less than a week, 4=six months or more) and how much of the time the individual experience fatigue (0=25% of the time, 3=all the time).

Euroqol-5D[43] is a 5-item self-report questionnaire assessing general health state on a 0 to 5 likert scale. It measures levels of problems with walking, performing self-care, doing usual activities, pain/discomfort, and anxiety/depression. It is widely used across Europe in assessments of health resources utilization as it allows measurement of Quality Adjusted Life Years (QALYs) in individuals presenting with a wide range of physical and mental disorders.

Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)[44] is a three-item self-report questionnaire assessing frequency of alcohol use (0=never, 4=four times each week or more), number of units typical for a drinking day (0=1-2 units, 4=10 or more units), and frequency of binge-drinking (0=never, 4=daily or almost daily). It is a short-version of the 10-item AUDIT developed by the World Health Organization.

Headache Impact Test – 6 (HIT-6)[45] is a six-item self-report questionnaire assessing intensity and consequences of headaches the last month, rated from never to always. The scale has a range from 36 to 78 with higher values indicating higher severity of headaches. The four headache impact severity categories are little or no impact (49 or less), some impact (50–55), substantial impact (56–59), and severe impact (60–78).

Work performance:

Work Productivity and Impairment Questionnaire General Health (WPAI:GH)[46] will be used to assess work performance and impairment in daily living. It is a six-item questionnaire that measures: sickness absenteeism; sickness presenteeism; overall work impairment and; activity impairment.

Cognitive function

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The Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) will be used to assess cognitive function. It is a 16-item self-reported instrument of subjective cognitive dysfunctions including executive function, processing speed, working memory, verbal learning and memory, attention/concentration and mental tracking. Items are rated using a 4-point scale. The higher the score, the more subjective complaints. Although the assessment was initially introduced for use with individuals with bipolar disorders, the rating can be used on other clinical populations.

Intervention-Related Assessments

The assessment package includes several brief self-report instruments that give insights into the expectation of and experiences associated with the intervention provided. These include:

Expectations: At baseline, one item scored on a 1 to 9 scale indicating to what extent the patient thinks a digital sleep intervention can work for them (1= not at all, 9 = perfectly).

Self-efficacy: At baseline, self-efficacy related to making behavioral changes will be assessed with a 13-item questionnaire scored on a 1 to 10 scale (1=not confident at all, 10=extremely confident). Seven items assess self-efficacy of behaviors related to CBT-I (e.g. following a plan for bed time and rise time), and six items assess self-efficacy in situations where it may be challenging to keep the behavioral changes (e.g. if you are depressed or feel hopeless, in weekends, etc).

The Negative Effects Questionnaire (NEQ)[47]: will be used to assess negative effects of digital interventions. The NEQ is a self-report measure that contains 20 items that are scored on a five-point Likert-scale (rated 0-4) where higher scores indicate higher levels of negative effects. After each item, the individual is asked whether they consider the effect to be caused by the intervention received or caused by other circumstances (yes/no), as well as one open-ended question.

Impact on future treatment: will be assessed post intervention with two items. The first will assess if this intervention has impacted motivation for face-to-face treatment for mental disorders, the second will assess if this intervention has impacted motivation for specifically working with sleep interventions at a later time (both scored on a 1 to 9 scale with 1=very demotivated, 9=very motivated).

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The Use of Sleep Strategies (USS): is a six item self-report questionnaire have been developed to assess how often individuals use six different therapeutic techniques (keep a stable rise time, refrain from sleeping during daytime, use the bed and bedroom only for sleeping, practiced sleep restriction, practiced stimulus control) and their perception of its utility. The techniques are integral to CBT-I but are also described in sleep psychoeducation or hygiene programmes.

Resource use and national registries

Using objective data available from national registries we will collate information on participants to allow to explore group differences before and/or after randomization-
a) reasons for referral;
b) diagnoses (International Statistical Classification of Diseases and Health Related Problems, ICD-10);
c) substance use, person injury (similar to Core minimum data set in World Health Organization (WHO) guidelines), incident leading to any hospital admission;
d) number of appointments at mental health care clinics, type and timing of treatment and admissions, and date of the first appointment for each patient during the study period (data on a-d from the *Norwegian Patient Registry (NPR));*
e) dose, timing and type of prescribed medications (According to the WHO Anatomical Therapeutic Chemical Classification System) and changes recorded during the RCT (data from *the Norwegian Prescription Database (NorPD));*
e) costs of treatment offered by the public services (data from the database named 'Kontroll og Utbetaling av Helserefusjon');
f) sick leave or in receipt of disability benefits (data from the administrative database called Forløpsdatabasen (FD Trygd);
g) cause of death (Dødsårsaksregisteret);

Subgroup data collection of objective sleep and circadian assessments

A subgroup of approximately 40 patients recruited at St Olavs Hospital will have concurrent assessments of sleep-wake patterns with actigraphy for 9 weeks during the intervention period.[49]

Actigraphy: Actigraphy is a wrist-worn accelerometer that can be used for assessment of

movement and indirectly as an objective assessment of sleep and circadian measures. [48] We will use GENEActive actiwatches (Activeinsights, Kimbolton, UK), which has a triaxial sensor for acceleration, a light sensor, and a temperature sensor.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-24+supplement 1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Supplement 1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies	4-6

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		(published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion),	9-12

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		and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, Fig. 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7, supplement 1
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training	6-12, supplement

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		of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9, 11

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Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13-14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 13-14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14

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Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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BMJ Open

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Primary Subject	Mental health

Heading:	
Secondary Subject Heading:	Mental health, Evidence based practice, Health services research
Keywords:	SLEEP MEDICINE, MENTAL HEALTH, PSYCHIATRY

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Abstract

Introduction: Insomnia is highly prevalent in outpatients receiving treatment for mental disorders. Cognitive Behavioural Therapy for Insomnia (CBT-I) is a recommended first-line intervention. However, access is limited and most patients with insomnia who are receiving mental health care services are treated using medication. This multi-centre randomized controlled trial (RCT) examines additional benefits of a digital adaptation of CBT-I (dCBT-I), compared with an online control intervention of Patient Education about insomnia (PE), in individuals referred to secondary mental health clinics.

Methods and analysis: A parallel group, superiority, RCT with a target sample of 800 participants recruited from treatment waiting lists at Norwegian psychiatric services. Individuals awaiting treatment will receive an invitation to the RCT, with potential participants undertaking online screening and consent procedures. Eligible outpatients will be randomized to dCBT-I or PE in a 1:1 ratio. Assessments will be performed at baseline, 9-weeks after completion of baseline assessments (post intervention assessment), 33-weeks after baseline (6 months after the post intervention assessment) and 61-weeks after baseline (12 months after the post intervention assessment). The primary outcome is between-group difference in insomnia severity 9-weeks after baseline. Secondary outcomes include between-group differences in levels of psychopathology, and measures of health and functioning 9-weeks after baseline. Additionally, we will test between-group differences 6 and 12 months follow-up, and examine any negative effects of the intervention, any changes in mental health resource use, and/or in functioning and prescription of medications across the duration of the study. Other exploratory analyses are planned.

Ethics and Dissemination: The study protocol has been approved by the Regional Committee for Medical and Health Research Ethics in Norway (Ref: 125068). Findings from the RCT will be disseminated via peer-reviewed publications, conference presentations and advocacy and stakeholder groups. Exploratory analyses, including potential mediators and moderators, will be reported separately from main outcomes.

ClinicalTrials.gov Identifier: NCT04621643; pre-results

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Strengths and limitations

- Use of an automated intervention in individuals awaiting assessment for face-to-face treatment for mental disorders could yield important information about how to stratify treatment interventions and offer insights into the role of sleep patterns in mental disorders.
- A large-scale multicentre trial, with broad eligibility criteria, undertaken in a public sector service increases the likelihood that findings are generalizable to other clinical settings.
- Sample size allows for detection of medium-small effect sizes on secondary outcomes.
- Limitations include potential sampling biases e.g. recruitment via self-ratings of insomnia rather than clinical evaluation.
- The sample comprises non-urgent referrals to mental health services, so translation of the findings to acutely ill psychiatric populations may be limited.

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Background

Insomnia is characterized by subjectively reduced sleep quality, in the form of delayed sleep onset or frequent or prolonged awakenings at night, and is associated with reduced daytime functioning.[1 2] It is highly prevalent in individuals with mental disorders.[3] In a study of more than 2000 secondary psychiatric outpatient clinic attendees in Norway, about 70% reported a concurrent sleep disturbance regardless of primary diagnosis; and 40% reported severe sleep difficulties.[4] Traditionally, insomnia has been regarded as a secondary problem that often arises among those experiencing a primary mental disorder. Recently, this view has been challenged, and the current edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) now advises clinicians to record "Insomnia Disorder" as an independent comorbidity (rather than a secondary diagnosis).[1] This change is important for clinical practice as it has increased the prominence of insomnia as a separate condition in psychiatric populations and draws attention to the sub-optimal outcomes of standard psychiatric treatments in individuals with co-occurring insomnia[5 6]. Further, it is increasingly clear that even when insomnia symptoms are a core symptom of the presenting syndrome, they may be more treatment refractory than other phenomena with 40%-70% of individuals who show improvement with antidepressants treatments continuing to report ongoing sleep difficulties.[7-11] Overall, clinicians and researchers now acknowledge the reciprocal relationship between sleep and mental disorders, such that they often perpetuate and exacerbate each other. This has raised awareness of the need to target interventions for insomnia, rather than assuming that it will simply be resolved following general psychiatric treatment.

While medications are employed for insomnia, there is reluctance to co-prescribe these medications with the complex regimes that are routinely used to treat mental disorders. Concerns range from their addictive potential, the risk of drug interactions especially with polypharmacy, and their low level of medium-to-long term effectiveness.[12] As such, there is a growing interest in the application of psychological interventions for insomnia, such as Cognitive Behavioural Therapy for Insomnia (CBT-I) which has a more favourable risk-to-benefit ratio and is a recommended first-line treatment for insomnia.[13 14] Further, several review articles and meta-analyses that synthesize data from randomized controlled trials (RCT) demonstrate that this intervention may also be effective in reducing sleep problems in individuals with comorbid physical and/or mental disorders.[15-19]

Taken together, it is clear that trials of CBT-I would be a useful addition to the knowledgebase regarding sleep and mental disorders. However, there is a paucity of trained CBT-I therapists and insufficient numbers of expert practitioners are available within specialist mental health services. This

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undermines the feasibility and utility of conducting large-scale RCTs relying on face-to-face therapy as it would be difficult to translate the findings to day-to-day practice. Self-guided, fully automated, digital CBT-I (dCBT-I) has been developed, tested and employed as a means of increasing access to the intervention to large, geographically spread populations. Automated dCBT-I has previously been shown to reduce insomnia severity among individuals with comorbid mental disorders in non-clinical populations,[20] to reduce depressive symptoms in individuals with sub-clinical depressive presentations,[21] - and across different sociodemographic groups.[22] Also, it appears to reduce psychotic symptoms in non-clinical samples.[23] These findings are encouraging and indicate that self-guided dCBT-I could be beneficial even in secondary care settings, such as mental health care outpatient clinics. One small trial in older men who were receiving psychiatric treatment for depression found that automated dCBT-I was effective in reducing insomnia severity 9 weeks after baseline assessment, and suggests a larger, longer-term trial is warranted.[24] Importantly, automated dCBT-I could be initiated immediately after an intake assessment (even if the individual is awaiting other interventions) and this strategy could potentially reduce the overall duration or intensity of specialist care.

Aims

The protocol outlines a two-arm, parallel-group, superiority RCT that examines the additional benefits of dCBT-I compared with a control intervention of digital patient education about insomnia (PE) offered over 9 weeks. This multi-centre RCT will recruit adults who have been referred to public sector secondary psychiatric outpatient clinics in Norway who are awaiting treatment of a mental disorder.

The overarching aim of the trial is to test the effectiveness of dCBT-I in a clinical, trans-diagnostic population of non-urgent referrals to adult psychiatric outpatient services. The primary endpoint is outcomes 9-weeks after the baseline assessment. This endpoint was selected because it allows sufficient time to complete the intervention, and the average wait-time before routine treatments commence is currently estimated at about 12 weeks, i.e. few patients will have initiated regular treatment by 9 weeks, allowing sufficient time for most participants to complete the key phase of the RCT prior to exposure to any specific psychiatric interventions that are proposed for the presenting condition. We will also assess outcomes 33- and 61-weeks after baseline assessments to test if there are any long-term gains or adverse effects associated with the experimental intervention.

The trial is designed to address the following hypotheses: Compared with PE, the dCBT-I intervention will, at each follow-up point (9-, 33- and 61-weeks after baseline assessment), be associated with:

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1) lower severity of self-reported symptoms of insomnia (primary outcome).
2) lower levels of self-reported psychopathology and somatic symptoms.
3) improved health and cognitive function.
4) less health resource utilization (operationalized as the number of treatment sessions received during the 12-month trial),
5) lower prescriptions rates for hypnotic, sedative/anxiolytic, and anti-depressant medications.

Secondary aims include analyses to test if there are specific subgroups that are more likely to benefit from dCBT-I; if exposure to dCBT-I or PE is associated with increased or reduced willingness to participate in face-to-face interventions for mental disorders in the future (e.g. individual treatment delivered by a therapist at a clinic or via telemedicine (if offered during COVID safety protocols are remain in place)); whether dCBT-I is associated with any negative effects; and/or whether dCBT-I is associated with any additional reduction in sick-leave, improved work productivity and daily activities outside of work.

Exploratory and additional analyses: We will perform mediation analyses, and plan to undertake cost-benefit analysis; longer term health and social outcomes (>12 month) will be assessed from objective data available via national registries. Also, participants recruited at the lead centre (St. Olavs Hospital, Trondheim) will be invited to participate in an actigraphy study examining objective recordings of sleep before, during, and after the intervention (target sample ~40).

Methods and analysis

The protocol for the RCT follows the SPIRIT guidelines (Standard Protocol Items for Randomized Trials)[25] and Figure 1 shows the flow chart for the recruitment and assessments. A completed SPIRIT checklist has been uploaded and a completed World Health Organization Trial Registration Data Set can be found in supplementary file 1.

Trial design

A multi-centre, parallel-group, superiority RCT of individuals who meet established criteria for clinically significant insomnia according to self-report assessments undertaken with the internationally-recognized standard rating. Trial participants will be randomized 1:1 to either dCBT-I or PE.

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Recruitment

Recruitment will be undertaken at psychiatric outpatient clinics located in public health care organizations ('health care trusts') across rural and urban areas in Norway. Individuals referred for assessment for outpatient treatment of a mental disorder at the participating clinics will be sent an invitation to join the RCT. The invitation will be sent when the patient is registered on the waiting list for commencing mental health treatment (also see the supplementary file 2 for additional details). This means that screening and randomization can be completed, and digital interventions commenced before the individual attends their first scheduled treatment session.

Eligibility

Individuals with an interest in participating will be directed to a website that provides information about the RCT. They will then be offered the opportunity to participate in the consent procedure and complete an online screening assessment for eligibility. Individuals who give written informed consent and meet trial inclusion criteria will receive a telephone call from an investigator who will answer any questions, ensure that potential participants received all the relevant written documentation about the RCT, and provide technical support regarding the digital intervention.

Inclusion criteria:

1. Individuals aged >= 18 years
2. Willing and able to provide written informed consent.
3. Insomnia Severity Index (ISI) > 11; (this cut-off score is employed as we have previously used it to identify individuals experiencing clinically significant insomnia and/or those who may benefit from dCBT-I[26]; also, it is the most sensitive to detect a diagnosis of Insomnia Disorder in a Norwegian sample[27]).

Exclusion criteria:

1. Sleep apnea screening: An Epworth Sleepiness Scale score >=13, indicative of high levels of objective daytime sleepiness associated with organic sleep disorders[28] and/or positive endorsement of a screening question for sleep apnoea (this asks if they "usually or everyday snore and stop breathing").
2. Medical history contra-indicating use of CBT-I, e.g. (i) epilepsy plus self-report of >=1 seizure

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within the preceding 12 months, or (ii) recent cardiac surgery, or (iii) currently in an attack phase of multiple sclerosis.

3. Individuals whose work schedule includes night shifts.
4. Pregnancy
5. Inadequate opportunity to sleep or living circumstances that prevent modification of sleep pattern (e.g. having an infant residing home).
6. Currently receiving psychological treatment for insomnia.
7. Not registered at or under the care of any of the trial centres.

Interventions

Digital CBT-I: CBT-I[29] is a multicomponent intervention that includes the following: psychoeducation about sleep, sleep hygiene, sleep restriction therapy, stimulus control and challenging dysfunctional beliefs and perceptions about sleep. This trial employs a digital CBT-I program named Sleep Healthy Using The internet (SHUTi),[20 30] which has been translated into Norwegian and employed in our previous RCTs.[31] SHUTi is fully automated and requires no contact with health care personnel and can be accessed on computers or hand-held devices using a browser-based interface. The program is interactive and comprises the same elements included in face-to-face CBT-I[29] (including tailoring of the program to individual needs). The user is provided with access to new educational, behavioral or cognitive modules in the week after completing a previous module. Between modules, users enter self-monitoring information into a digital sleep diary.

Digital patient education about insomnia (PE): The PE offers digital sleep hygiene information that can be accessed on computers or hand-held devices and has been used in multiple RCTs of SHUTi for insomnia.[20 26 30 31] There is some content overlap with that included in the dCBT-I intervention, but it does not include any of the interactive features of the dCBT-I intervention and all the information is available to the user from the outset.

Randomization

This RCT employs the same randomization procedure as in a previous Norwegian trial of dCBT-I.[26] The automated procedure involves block randomization with varying block sizes and cannot be influenced in any way by the researchers. Participants are blinded to their group allocation, but complete blinding is not possible as the participants may be able to discern whether they have received the active or control condition.

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Withdrawal

Participants will be informed that they can withdraw from the trial at any time, without stating any reason and without any consequences whatsoever for their mental health treatment.

Crisis management procedure

All clinics have an emergency psychiatric service (24/7) for patients who require immediate assistance, experience crises, distressing increases in symptoms and/or marked deteriorations in functioning. This service is responsible for all clinic attendees, including trial participants. If any trial participant utilizes the emergency service, the investigators will be informed and a decision made regarding continuation in the RCT and/or whether the crisis constitutes a trial-related adverse event.

Outcome assessments

The trial will adhere to the recommended standards for the research assessment of insomnia.[32] Self-report questionnaires will be completed online at baseline, post assessment (9 weeks after baseline), 6 months after the post assessment (33 weeks after baseline) and 12 months after the post assessment (61 weeks after baseline). Table 1 summarizes the type and timing of all assessments (also see the supplementary file 3 for additional details). Individuals will receive an automated message prompting them to complete the relevant online assessments at each time point

Demography and Clinical Characteristics

As shown in Table 1, key demographic information will be recorded at baseline.

Self-reported clinical history will include information about sleep problems, medication use, previous medical, mental, and physical disorders, treatments, and admissions. Data will also be collected regarding type and number of physical disorders (from a list of 20 common medical conditions) and mental disorders (from a list of 9 common mental disorders).

Sleep measures:

Primary outcome measure:

The Insomnia Severity Index[33] is a 7-item questionnaire assessing the severity of insomnia symptoms the last 14 days.

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Secondary outcome measures:

Other measures of sleep and chronotype:

The Consensus Sleep Dairy[34] assesses prospective daily sleep-wake patterns on at least 10 of 14 consecutive days.

The Reduced Morningness – Eveningness Questionnaire[35] measures chronotype i.e. time preference for daily activities, including bed-times.

Bergen Insomnia Scale[36] assesses symptoms of insomnia based on the insomnia criteria in the DSM-IV.[37]

Level of psychopathology & functional impairment:

The Outcome Questionnaire – 45.2[38] assesses mental health status, including symptom distress, interpersonal relations, and social role functioning.

The Hospital Anxiety and Depression Scale[39] assesses non-vegetative symptoms of anxiety and depression.

Nightmares and nocturnal mentation:

Selected items from the *Nightmare Frequency Questionnaire*[40], *Nightmare intensity*[41] and *Nocturnal mentation*[42] questionnaires will be used to assess frequency and intensity of nightmares and nocturnal mentation.

Measures of somatic symptoms and health

The Chalder Fatigue Scale[43] assesses levels of daytime physical and psychological fatigue.

Euroqol-5D[44] assesses general health state and allows measurement of Quality Adjusted Life Years in individuals presenting with a range of physical and mental disorders.

Alcohol Use Disorders Identification Test – Consumption assesses the frequency and amount of alcohol use.

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Headache Impact Test – 6[45] assesses the intensity and consequences of headaches the last month.

Work performance:

Work Productivity and Impairment Questionnaire General Health[46] assesses work performance and impairment in daily living.

Cognitive function

The Cognitive Complaints in Bipolar Disorder Rating Assessment assesses subjective cognitive function.

Intervention-Related Assessments

Expectations: one item assessing to what extent the patient thinks a digital sleep intervention can work for them (1= not at all, 9 = perfectly).

Self-efficacy: At baseline, a questionnaire assessing self-efficacy related to making behavioural changes.

The Negative Effects Questionnaire (NEQ)[47] assesses negative effects of digital interventions.

Impact on future treatment: two items assesses if exposure to digital interventions has impacted on willingness to participate in face-to-face therapy for mental disorders, and/or sleep problems.

The Use of Sleep Strategies assesses how often individuals use different therapeutic techniques for sleep and their perception of its utility.

Resource use and national registries

Using objective data available from national registries we will collate information on participants to allow to explore group differences before and/or after randomization-

a) reasons for referral;

b) diagnoses;

c) substance use, person injury, incident leading to any hospital admission;

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d) appointments, treatments and admissions at mental health care clinics;

e) dose, timing and type of prescribed medications and changes recorded during the RCT;

e) costs of treatment offered by the public services;

f) sick leave or in receipt of disability benefits;

g) if any deaths occur during the course of the study, we will record the cause (as recorded on the death certificate).

Subgroup data collection of objective sleep and circadian assessments

About 40 participants recruited at St Olavs Hospital will be invited to undertake concurrent actigraphy monitoring of sleep-wake patterns.[48]

Sample size

The primary outcome is difference in ISI scores at 9 weeks post-baseline. Published RCTs of CBT-I or dCBT-I report an effect size (ES) (Cohen's d) between 0.8-2.0 for these interventions compared with control conditions for community samples or clinical trials in populations with insomnia. However, we anticipate digital interventions may not have such a large effect in a trans-diagnostic psychiatric outpatient population,[24] so we have estimated the RCT sample size based on a Cohen's $d = 0.5$. Additionally, we wanted the sample size to provide adequate statistical power to detect small to moderate ES (Cohen's $d = 0.3$ to 0.5) on the secondary outcomes (levels of psychopathology, etc). Lastly, other RCTs of CBT-I report sample attrition rates of between 12% and 50%.[20 21] As the planned RCT involves limited contact between investigators and participants and has a 12-month follow-up, we have assumed a study dropout rate of about 50%. Therefore, we aim to recruit 800 participants, to enable us to retain 400 patients (200 in each treatment arm) at the end of the RCT. For a two-sample t-test with alpha=0.05, this sample size gives a power of 99.9%, 93.7%, and 84.9% of detecting a difference of Cohen's $d = 0.50$, 0.40, and 0.30, respectively.

We did not undertake any statistical power calculations related to the analysis of service utilization, medication use etc., as assessed in the National Registers, or cost-benefit analysis. Missing data is unlikely to be an issue when examining the National Registers.

Statistical analytic plan

Descriptive statistics. Summary descriptions of demographic and clinical characteristics will be presented for each group. Categorical and binary variables will be presented as counts and percentages,

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continuous variables will be presented as means and standard deviations or medians and interquartile ranges, as appropriate.

Analysis of primary and secondary outcomes. The key outputs will be intention to treat analyses, i.e. everyone who is randomized will be analyzed. Per-protocol analyses will be reported for individuals who complete >=4 dCBT-I modules. There will be no planned interim analyses during the inclusion period, though we will publish findings from self-reported data prior to the registry data.

We plan to use linear mixed model analysis to examine the difference between the two randomized groups on the primary and secondary outcomes with continuous variables. The model will include time, group, time-group interaction, and baseline covariates. For binary secondary outcomes, logistic mixed model analysis will be used. Linear mixed models (logistic mixed models) provide unbiased (approximately unbiased) results when the data are missing at random (MAR). Model assumptions will be reviewed and if the assumptions are not met, this will be handled using bootstrapping, logarithmic transformations, or analysed using non-parametric testing as appropriate. We will assess the influences of deviations from MAR in sensitivity analyses as described below.

Mediation and moderator analysis. In order to identify if changes in insomnia symptoms, levels of psychopathology, or cognitive function are important mediators of the effect of the digital treatment, we will perform mediation analyses assessing following the conceptual principles described by Kraemer et al.[49]

Sensitivity analysis. To investigate the influence of deviations from the MAR assumption, we will use a pattern-mixture models (PMMs) to simulate a range of situations where the data for both primary and selected secondary outcome variables are missing not at random (MNAR).

Ethics and dissemination

The protocol has been approved by by the Regional Committee for Medical and Health Research Ethics in Norway, REK Sør-Øst B (Ref: 125068). The RCT follows the guidance and principles outlined in the Revised Declaration of Geneva.[50] All eligible participants will be required to give online written informed consent before study entry, please see supplement 4 for a copy. Participants will be provided with written and printable information regarding the RCT, which will also be repeated in a telephone call with an investigator. Both the written and oral information emphasize that participation

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is voluntary, that individuals will receive the same standard of care and treatment at the mental health clinic regardless of their participation, that they may withdraw from the trial at any time without any consequences for their clinical care and that they do not need to give a reason for withdrawal.

Self-report data will be de-identified and stored in encrypted and password protected databases that are compliant with the General Data Protection Regulation (GDPR). Data from National Registries will be downloaded and incorporated into the files and anonymized.

The findings from the RCT will be disseminated via conference presentations and peer-reviewed scientific publications. The first academic publication will report any between-group differences on self-reported outcomes. Subsequent academic publications will report findings related to data extracted from the national registries, health economic analyses and mediation and moderation analyses. The investigators will adhere to international guidelines regarding multi-authorship of manuscripts.

Patient and public involvement

The service user group for mental health care at the Central Norwegian Health Trust were consulted regarding the study outline and provided feedback on the aims of the trial and the assessments included in the protocol.

Study monitoring

A Data and Safety Monitoring Committee will meet weekly initially (during the start-up phase), and then monthly to oversee study progress, technical issues, status at the included sites and any reports of severe side effects. Other meetings can be convened if a specific problem or serious and untoward incident is reported. The committee comprises the project leader, project coordinator, and the investigators involved with overseeing recruitment and eligibility. Clinical representatives from participating health care hospital trusts, statistical advisors, administrative leaders, and other representatives will be co-opted as needed. The trial sponsor and the included health care trusts routinely and randomly audits one or more ongoing projects each year. The audit process ensures that trial protocols are followed, and ethical standards upheld. If any important protocol amendments are necessary, these will first be evaluated by the ethics committee and published on relevant study websites.

Discussion

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The utility of dCBT-I, and its impact on insomnia, psychopathology, cognitive functioning, and general health in routine clinical settings is not yet established. Given the bidirectional relationship between and sleep and mental disorders, interventions that are effective in reducing insomnia severity may also have benefits for comorbid psychiatric conditions.[51-53] For instance, one meta-analysis of CBT-I for insomnia in individuals with physical and mental disorders reported small to moderate effect sizes on comorbid symptoms with larger effects for psychiatric symptoms,[19] while another meta-analysis demonstrated small to medium ES for the effect of CBT-I on depressive symptoms.[54] It is possible that improvement in sleep early in the treatment process could lead to earlier response and/or improved outcomes of the presenting mental disorder. While findings of CBT-I research are encouraging, it is noteworthy that many RCTs do not have adequate statistical power to enable detection of effects on a broader range of symptoms and phenomena (beyond sleep), while others have been conducted in convenience or non-clinical samples. This means the effects of CBT-I on sleep in many mental health treatment settings are unclear. The current RCT aims to address some of these knowledge gaps, the sample size is calculated to allow detection of small-medium effect sizes on these secondary outcomes, and the trial is conducted in a trans-diagnostic clinical sample.

There are scientific limitations associated with conducting an RCT in heterogenous clinical samples attending different outpatient settings. First, diagnoses will be recorded by the clinicians at the clinics and not by the investigators, and there may be between-clinic differences in how some diagnoses are recorded. Also, there may be variability between clinics and between diagnostic subgroups regarding the waiting time for a first treatment session. Whilst most patients are likely to complete the course of dCBT-I before routine psychiatric outpatient treatment commences, others may experience an overlap between interventions. Thus, the trial may be a test of the effectiveness of dCBT-I when offered at an early stage of psychiatric treatment rather than prior to the introduction of routine care. Moreover, secondary psychiatric services, and health care policies are continuously evolving, and it is conceivable that outpatient assessment and treatment protocols might change after the RCT has begun. Finally, there are 20 outpatient clinics that have agreed to recruit participants to the trial, but most have not been able to do any piloting of the protocol (partly due to COVID, etc). We do not know how much recruitment will differ between urban and rural areas in Norway, and/or if additional clinics will need to be added (e.g. if recruitment is behind expected rates). This precludes using randomization sequences that are stratified according to clinic. Despite these limitations, we believe the results of this trial will be important in moving the field forwards in its understanding of the feasibility and utility of

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fully automated dCBT-I in clinical samples of psychiatric outpatients with a wide range of mental disorders, and how treatment of insomnia can affect other important clinical and social outcomes.

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Conflict of interest

Lee Ritterband report financial or business interests in BeHealth Solutions and Pear Therapeutics, two companies that develop and disseminate digital therapeutics (including by licensing the therapeutic developed) based in part on early versions of the software from the University of Virginia, which is used in the research reported in this Article. These companies had no role in preparing this manuscript. Dr. Ritterband is also a consultant to Mahana Therapeutics, a separate digital therapeutic ompany not affiliated with this research. The terms of these arrangements have been reviewed and approved by the University of Virginia in accordance with its policies. All other authors declare no competing interests.

Author statement

Study design was undertaken by the research team: HK, SBS, ØV, KL, GM, SL, MRS, SKD, BH, SGS, KH, TCS, AGH, LR, BS, and JS. HK conceived of the study and produced the first draft of the protocol paper with additional input form SBS, ØV, and JS. SL and MRS wrote the statistical analytic plan. All authors contributed to the drafting of the submitted version of the study protocol and all authors approved the final version of manuscript.

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Table 1: Key measures and timing of assessment

	Screening &/or Baseline	9-week follow-up	33-week follow-up	61- week follow-up
Demography & Clinical Characteristics				
Demographics (Age, Sex, Ethnicity)	X			
Marital status	X		X	X
Number of children living at home	X		X	X
Years of education	X			
Employment status	X	X	X	X
Medication use	X	X	X	X
Duration of sleep problems	X			
Previous treatments for mental disorders	X			
Previous treatments for insomnia	X			
Previous psychiatric hospital admissions	X			
Physical health	X			
Mental health	X			
Sleep and Circadian Rhythms*				
Insomnia Severity Index (ISI)	X	X	X	X
Brief Morningness Eveningness Questionnaire (rMEQ)	X		X	X
Consensus Sleep Diary	X	X	X	X
Bergen Insomnia Scale (BIS)	X	X	X	X
Epworth Sleepiness Scale (ESS)	X			
Level of psychopathology				
Outcome Questionnaire – 45.2 (OQ-45.2)	X	X	X	X
Hospital Anxiety & Depression Scale (HADS)	X	X	X	X
Nightmares and nocturnal mentation				
Nightmare Frequency Questionnaire (NFQ)	X	X	X	X
Nightmare intensity (CAPS)	X	X	X	X
Nocturnal mentation (DRFS)	X	X	X	X
Somatic symptoms and health				
Chalder Fatigue Questionnaire (CFQ)	X	X	X	X
EuroQol (EQ-5D)	X	X	X	X
Body Mass Index	X	X	X	X
Alcohol Use Identification Test - Consumption (AUDIT-C)	X	X	X	X
Headache Impact Test – 6 (HIT-6)	X	X	X	X
Cognitive function				
Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)	X	X	X	X
Intervention related assessments				
Treatment expectations	X			
Self-efficacy for sleep related behavioral change	X	X		
The Negative Effects Questionnaire (NEQ-20)		X		
Impact on future treatment		X		
Use of Sleep Strategies		X	X	X
Work Capacity & Resource Use (Registry data)				
Work Productivity and Impairment Scale (WPAI)	X	X	X	X
Health service utilization and ICD-10 diagnoses	X			X
Prescribed medications	X			X
Number of hospital admissions (and reasons)				X
Resource use				X
Cause of death				X

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*NB: Actigraphy data will be collected at each timepoint for sample recruited via St. Olavs University Hospital.

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Figure 1. Flow chart of timeline for a randomized controlled trial of digital interventions for insomnia.

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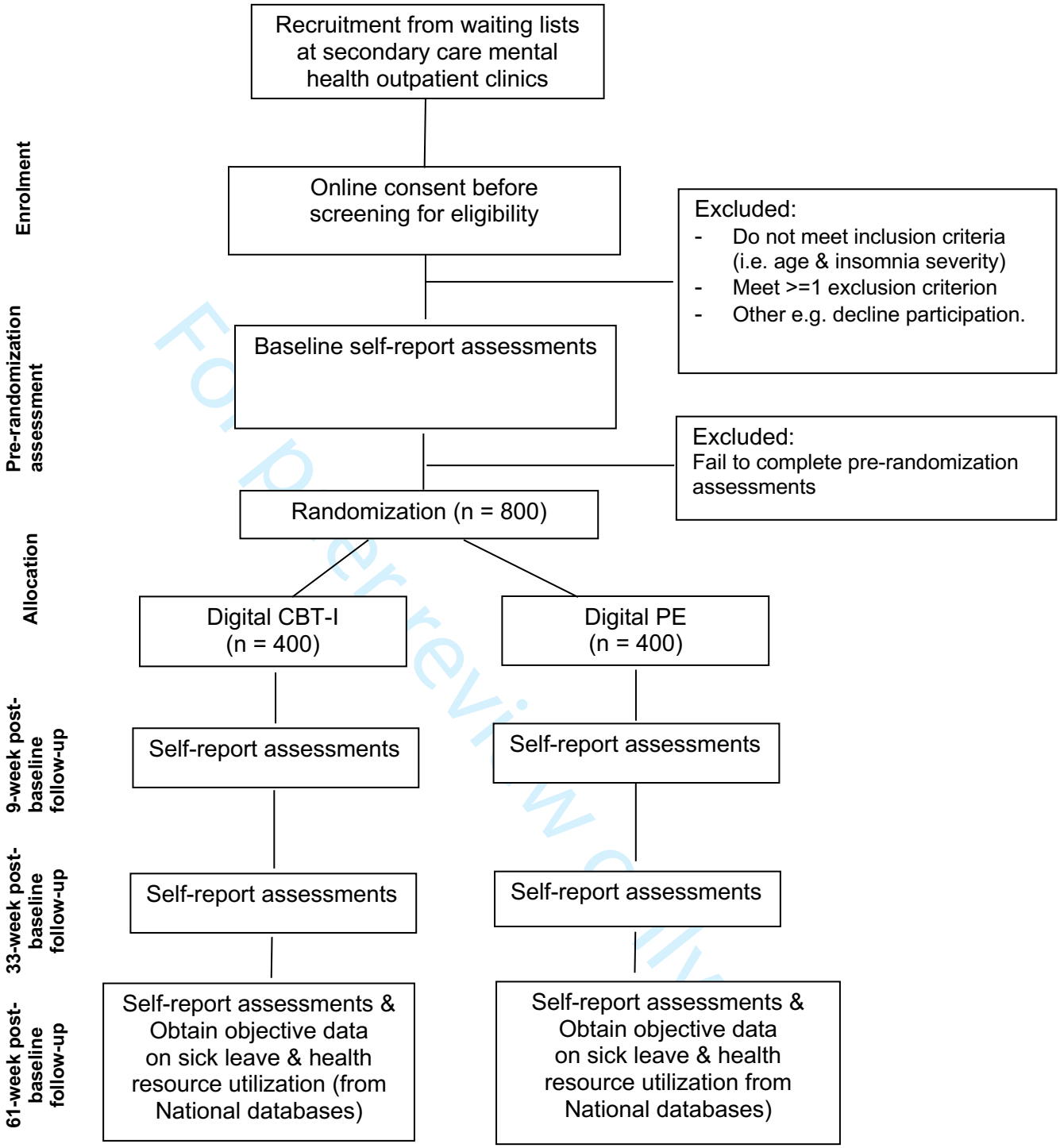

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SUPPLEMENT 1

Title: *Protocol for a multi-center randomized controlled trial of digital cognitive behavior therapy for insomnia compared with digital patient education about insomnia in individuals referred to secondary mental health services in Norway.*

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World Health Organization Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	CinicalTrials.gov: NCT04621643
Date of registration in primary registry	November 9, 2020
Secondary identifying numbers	Regional Committees for Medical and Health Research Ethics in South East Norway (125068).
Source(s) of monetary or material support	The Norwegian Research Council, grant number 273623
Primary sponsor	St. Olavs University Hospital (stolav.no)
Secondary sponsor(s)	None
Contact for public queries	HK (havard.kallestad@ntnu.no), SS (Simen.b.saksvik@ntnu.no), ØV (oystein.vedaa@ntnu.no)
Contact for scientific queries	HK (havard.kallestad@ntnu.no)
Public title	A digital intervention for insomnia for outpatients in mental health care.
Scientific title	A multi-center randomized controlled trial of digital cognitive behavior therapy for insomnia compared with digital patient education about insomnia in individuals referred to secondary mental health services in Norway.
Countries of recruitment	Norway
Health condition(s) or problem(s) studied	Mental Disorders, Insomnia
Intervention(s)	Active treatment: Digital Cognitive Behavior Therapy for Insomnia (Sleep Healthy Using The internet, SHUTi).
	Comparator: Digital patient education about insomnia
Key inclusion and exclusion criteria	Inclusion: Age >= 18 years old. Score on the Insomnia Severity Index >= 12. Willing and able to provide consent.
	Exclusion criteria: Individuals scoring >= 13 on the Epworth Sleepiness Scale (ESS), and/or answering that they usually or every day snore and stop breathing (i.e., they positively endorse pre-selected indicators of sleep apnoea); self-report of the presence of any medical conditions where a fully automated CBT-I may be contra-indicated (e.g. epilepsy, recent heart surgery); and/or participating in shift work; and/or pregnancy; and/or having inadequate opportunity to sleep; and/or currently receiving psychological treatment for insomnia, and/or not registered at or under the care of any of the trial centers
Study type	Interventional
	Allocation: Randomized intervention model. Parallel assignment model: Blind (subject)
	Primary purpose: Intervention
Date of first enrolment	December 2020
Target sample size	800
Recruitment status	Recruiting
Primary outcome(s)	The Insomnia Severity Index
Key secondary outcomes	Sleep Diaries, Mental health, Physical Health, Nocturnal mentation, Cognitive function, Diurnal preference, Work productivity, Sick leave, Medication use, Health resource use.

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SUPPLEMENT 2

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Recruitment

All individuals will be patients who have been referred to treatment for a mental disorder at one of the secondary outpatient clinics. As part of the standard routine in public mental health care outpatient clinics, these referrals, along with all other available patient information, are evaluated to establish if 1) the patient's mental health condition is severe enough to warrant treatment in secondary health care, of so 2) if it is an urgent or non-urgent case, i.e. if there is an acute suicide risk or other risk for severe deterioration of condition. In urgent cases, the patients are offered emergency treatment in mental health care. The non-urgent patients are placed on a waiting-list to receive treatment for their condition at the clinic and will be sent written information about this, their patient rights, and instructions for who to contact in case the patient experience a deterioration of the condition in the waiting period. This is sent to the patient and their General Practitioner by the clinic (by mail and/or electronically) immediately after the evaluation team have made their decision, usually the same day. This procedure follows the guidelines by the Norwegian Directorate of Health. In the written information the patients at the participating clinics will additionally receive information about this trial and a description of where to find the trial website. This means that non-urgent patients will be invited and screening and randomization can be completed and the digital interventions will have commenced before the individual attends their first formal clinical treatment session.

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SUPPLEMENT 3

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Outcome assessments

Sleep measures:

Primary outcome measure:

The Insomnia Severity Index (ISI)[31] is a 7-item questionnaire assessing the severity of insomnia symptoms the last 14 days. Each item is rated on a 0 to 4 rating scale with higher scores indicating more severe symptoms. The ISI has good psychometric properties and is validated for online use.[32] Range is 0-28 with higher values represent higher levels of insomnia symptom severity. A cut-off of 7 or below is used to indicate normal sleep and used to indicate remission after the interventions, and a reduction of 8 points during the interventions is used to indicate response to the intervention.[31]

Secondary outcome measures:

Other measures of sleep and chronotype:

Consensus Sleep Dairy: Prospective daily sleep-wake patterns will be assessed with the consensus sleep diary[33] which will be completed by the participant at baseline and each follow-up point for at least 10 out of 14 consecutive days. Individuals will be asked to record their bed-time, sleep onset latency, wake after sleep onset, number of nocturnal awakenings, time of final awakening in the morning, and rise-time, in addition sleep quality will be rated on a 5-point scale (with a higher score indicating better sleep quality).

Reduced (also known as Brief) Morningness – Eveningness Questionnaire (rMEQ): The rMEQ is a widely used measure of chronotype i.e. time preference for daily activities, including bedtimes. The rMEQ has five items yielding scores from 4 to 25, with lower scores indicating a preference for "eveningness" and higher scores indicating a preference for "morningness". Scores can be categorized as: definitely evening type (score <8), moderately evening type (score 8-11), neither type (score 12-17), moderately evening type (score 18-21), and definitely morning type (score >21).[34]

Bergen Insomnia Scale[35]*:* comprises six items that assesses symptoms of insomnia based on the insomnia criteria found in the Diagnostic and Statistical Manual of Mental Disorders-IV-TR (American Psychiatric Association).[36]

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Level of psychopathology & functional impairment:

The Outcome Questionnaire – 45.2 (OQ-45.2) is a 45 item self-report scale assessing mental health status. The scale is specifically designed for assessing patient progress throughout therapy and is widely used clinically, and as an outcome measure in clinical trials. It has excellent internal consistency and is shown to be highly correlated with well-known outcomes such as the Symptom Checklist 90R, Beck Depression Inventory, The State Trait Anxiety Inventory, The inventory of interpersonal problems, The Social Adjustment Scale, and the SF-36.[37] The scale is scored on a scale of 0 (=never) to 5 (=almost always) giving a range of 0 to 180, with higher scores indicating higher levels of psychopathology. The OQ-45.2 has three validated subscales: symptom distress, interpersonal relations, and social role functioning (perceived level of difficulties in the workplace, school or home duties). Results will be reported for the sum score, and for the three subscales. The OQ-45.2 has an established clinical cut-off value and reliable change index.[37]

The Hospital Anxiety and Depression Scale (HADS)[38] is a 14-item questionnaire assessing non-vegetative symptoms of anxiety and depression on a 0 to 3 likert scale. The sum score can be used as a measure of general psychological distress and is widely used in the community, general practice and psychiatric settings. It has a range of 0 to 42 points with higher scores indicating higher levels of psychological distress.

Nightmares and nocturnal mentation:

The Nightmare Frequency Questionnaire (NFQ)[39]: One item from the NFQ assessing of frequency of nights with nightmares (in days per week, month or year).

Nightmare intensity[40]*:* One item from the clinical administered PTSD-scale (CAPS)[40] assessing the intensity of nightmares on a four point Likert-type scale ranging from 1 (= minimal) to 4 (=extreme).

Nocturnal mentation[41]*:* Three items from the Dream Recall Frequency Scale (DRFS) are used to assess nocturnal mentation and can be used as a proxy for REM sleep fragmentation.[41] The items are scored on a 0 (=never) to 8 (=almost every day/night) and assess how often the participant is aware of having thoughts during sleep, how often night-time thoughts affect mood next day, and how often the participant tells others about their night-time thoughts, giving a total score of 0 to 24.

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Measures of somatic symptoms and health

The Chalder Fatigue Scale (CFS)[42] is a 11-item questionnaire assessing levels of daytime physical and psychological fatigue on a 0 to 3 likert scale (0=less than usual, 3=much more than usual). The scale has a range of 0 to 33 with higher scores indicating higher levels of fatigue. Two additional items assess duration of fatigue (0=less than a week, 4=six months or more) and how much of the time the individual experience fatigue (0=25% of the time, 3=all the time).

Euroqol-5D[43] is a 5-item self-report questionnaire assessing general health state on a 0 to 5 likert scale. It measures levels of problems with walking, performing self-care, doing usual activities, pain/discomfort, and anxiety/depression. It is widely used across Europe in assessments of health resources utilization as it allows measurement of Quality Adjusted Life Years (QALYs) in individuals presenting with a wide range of physical and mental disorders.

Alcohol Use Disorders Identification Test – Consumption (AUDIT-C)[44] is a three-item self-report questionnaire assessing frequency of alcohol use (0=never, 4=four times each week or more), number of units typical for a drinking day (0=1-2 units, 4=10 or more units), and frequency of binge-drinking (0=never, 4=daily or almost daily). It is a short-version of the 10-item AUDIT developed by the World Health Organization.

Headache Impact Test – 6 (HIT-6)[45] is a six-item self-report questionnaire assessing intensity and consequences of headaches the last month, rated from never to always. The scale has a range from 36 to 78 with higher values indicating higher severity of headaches. The four headache impact severity categories are little or no impact (49 or less), some impact (50–55), substantial impact (56–59), and severe impact (60–78).

Work performance:

Work Productivity and Impairment Questionnaire General Health (WPAI:GH)[46] will be used to assess work performance and impairment in daily living. It is a six-item questionnaire that measures: sickness absenteeism; sickness presenteeism; overall work impairment and; activity impairment.

Cognitive function

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The Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) will be used to assess cognitive function. It is a 16-item self-reported instrument of subjective cognitive dysfunctions including executive function, processing speed, working memory, verbal learning and memory, attention/concentration and mental tracking. Items are rated using a 4-point scale. The higher the score, the more subjective complaints. Although the assessment was initially introduced for use with individuals with bipolar disorders, the rating can be used on other clinical populations.

Intervention-Related Assessments

The assessment package includes several brief self-report instruments that give insights into the expectation of and experiences associated with the intervention provided. These include:

Expectations: At baseline, one item scored on a 1 to 9 scale indicating to what extent the patient thinks a digital sleep intervention can work for them (1= not at all, 9 = perfectly).

Self-efficacy: At baseline, self-efficacy related to making behavioral changes will be assessed with a 13-item questionnaire scored on a 1 to 10 scale (1=not confident at all, 10=extremely confident). Seven items assess self-efficacy of behaviors related to CBT-I (e.g. following a plan for bed time and rise time), and six items assess self-efficacy in situations where it may be challenging to keep the behavioral changes (e.g. if you are depressed or feel hopeless, in weekends, etc).

The Negative Effects Questionnaire (NEQ)[47]: will be used to assess negative effects of digital interventions. The NEQ is a self-report measure that contains 20 items that are scored on a five-point Likert-scale (rated 0-4) where higher scores indicate higher levels of negative effects. After each item, the individual is asked whether they consider the effect to be caused by the intervention received or caused by other circumstances (yes/no), as well as one open-ended question.

Impact on future treatment: will be assessed post intervention with two items. The first will assess if this intervention has impacted motivation for face-to-face treatment for mental disorders, the second will assess if this intervention has impacted motivation for specifically working with sleep interventions at a later time (both scored on a 1 to 9 scale with 1=very demotivated, 9=very motivated).

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The Use of Sleep Strategies (USS): is a six item self-report questionnaire have been developed to assess how often individuals use six different therapeutic techniques (keep a stable rise time, refrain from sleeping during daytime, use the bed and bedroom only for sleeping, practiced sleep restriction, practiced stimulus control) and their perception of its utility. The techniques are integral to CBT-I but are also described in sleep psychoeducation or hygiene programmes.

Resource use and national registries

Using objective data available from national registries we will collate information on participants to allow to explore group differences before and/or after randomization-
a) reasons for referral;
b) diagnoses (International Statistical Classification of Diseases and Health Related Problems, ICD-10);
c) substance use, person injury (similar to Core minimum data set in World Health Organization (WHO) guidelines), incident leading to any hospital admission;
d) number of appointments at mental health care clinics, type and timing of treatment and admissions, and date of the first appointment for each patient during the study period (data on a-d from the *Norwegian Patient Registry (NPR));*
e) dose, timing and type of prescribed medications (According to the WHO Anatomical Therapeutic Chemical Classification System) and changes recorded during the RCT (data from *the Norwegian Prescription Database (NorPD));*
e) costs of treatment offered by the public services (data from the database named 'Kontroll og Utbetaling av Helserefusjon');
f) sick leave or in receipt of disability benefits (data from the administrative database called Forløpsdatabasen (FD Trygd);
g) cause of death (Dødsårsaksregisteret);

Subgroup data collection of objective sleep and circadian assessments

A subgroup of approximately 40 patients recruited at St Olavs Hospital will have concurrent assessments of sleep-wake patterns with actigraphy for 9 weeks during the intervention period.[49]

Actigraphy: Actigraphy is a wrist-worn accelerometer that can be used for assessment of

movement and indirectly as an objective assessment of sleep and circadian measures. [48] We will use GENEActive actiwatches (Activeinsights, Kimbolton, UK), which has a triaxial sensor for acceleration, a light sensor, and a temperature sensor.

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SUPPLEMENT 4

Title: *Protocol for a multi-center randomized controlled trial of digital cognitive behavior therapy for insomnia compared with digital patient education about insomnia in individuals referred to secondary mental health services in Norway.*

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DO YOU WANT TO PARTICIPATE IN THE RESEARCH PROJECT: 'DIGITAL SLEEP TREATMENT FOR INDIVIDUALS REFERED TO PUBLIC MENTAL HEALTH SERVICES'

WHAT IS THE PROJECT ABOUT?

You are invited to participate in a research project to try digital (internet-based) treatment for chronic sleep problems (insomnia).

Insomnia involves problems falling or staying asleep. Although insomnia is highly prevalent among persons with mental health disorders, it is very uncommon to receive non-pharmaceutical treatment for these problems. In this study we aim to establish an effective and accessible treatment for insomnia delivered through the internet. You will get access to the treatment via an internet page, accessible via a computer or a smart phone.

To be eligible for this study you must be over 18 years of age and be referred to treatment at a public mental health clinic ("distrikspsykiatrisk sykehus, DPS") in Norway.

This study is a collaboration project between NTNU, Folkehelseinstituttet, St. Olavs Hospital St. Olavs Hospital (Nidaros DPS, Tiller DPS, Orkdal DPS), Akershus universitetssykehus (Follo DPS, Groruddalen DPS, Nedre Romerike DPS, Øvre Romerike DPS), Helse Stavanger (Stavanger DPS, Sola DPS, Sandnes DPS), Helse Nord-Trøndelag (Namsos Sykehus, Levanger Sykehus, Stjørdal DPS), Helse Møre og Romsdal (Molde DPS, Kristiansund DPS, Ålesund DPS, Volda DPS), Helse Bergen (Kronstad DPS, Voss DPS), Vestre Viken (Bærum DPS), Oslo Universitetssykehus (Søndre Oslo DPS, Nydalen DPS), the University of Virginia and the University of California, Berkeley (USA). The project leader is psychologist Håvard Kallestad, PhD at St.Olavs Hospital

WHAT DOES THE STUDY INVOLVE?

The study period is 12 months and the sleep treatment lasts for 6-8 weeks. We will register information about you to investigate the effect of the sleep treatment.

We will ask you to complete questionnaires before the treatment as well as nine weeks, 6 months and 12 months after the treatment started (see time schedule in Chapter A). Registered personal information are contact information (name and address) and demographic information (sex, age and education). We will also ask about your general health, mental health, sleep habits and daily activity and habits. Your sleep pattern will be registered with a sleep diary which is a short form you can complete via the internet and takes about 2-3 minutes to complete.

To participate in this study you must first answer a short screening form via the internet. In this form it will be evaluated whether you have sleep problems and if you meet the criteria for participation. This form will start immediately after you have signed this consent form. If you are qualified for participation and consent to participate you will receive messages and get a phone call from the study administration prior to and after the treatment. The purpose of these contacts will be to give an oral presentation of what the study involves, to answer questions you may have regarding your participation in the study, to remind you to complete the questionnaires and to answer potential technical questions.

Before the treatment starts you will be randomized into one of two possible treatment groups. Both groups have previously been shown to have a good treatment effect on sleep problems in prior research:

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Group 1: In this group you will get access to a web page with relevant information about insomnia and good sleep habits.

Group 2: In this group you will get access to an internet-based treatment-program, designed to give individually adjusted instruction about how to improve your sleep. You will receive weekly assignments to complete. You must complete sleep diaries throughout the whole treatment period (6 weeks)

Participants who live in Trondheim will be contacted and asked to complete additional measurements of sleep and daytime activity with equipment fastened to the wrist (actigraphy). These participants will be specifically contacted about this.

POTENTIAL ADVANTAGES, DISADVANTAGES AND SERIOUS ADVERSE EVENTS

Your participation in this study will not have any consequences for your treatment options at the DPS. This study is an offer you receive in addition to the ordinary treatment at the DPS.

The advantage of participating in this study is that you may get a notably better sleep quality after treatment which may reduce your daytime sleepiness and improve your mood. Your participation may also improve the treatment options for insomnia in Norway, that you and others can receive in the future. A potential disadvantage with a participation in this study is that the program requires effort and time, and some may find this challenging. A part of the treatment may require that your time in bed is restricted for a short period which may result in a short period with a shorter sleep time and increased sleepiness.

VOLUNTARY PARTICIPATION

Participation in the study is voluntary. If you wish to participate, sign the declaration of consent at the bottom of the page. You can withdraw your consent to participate in the study at any time and without stating any particular reason. If you do not wish to participate in the study or wish to withdraw from the study this will not have any consequences for you or your future treatment options. If you withdraw your consent, we will stop the research on your health information. You can also demand to have your health information to be deleted or delivered to you within 30 days. The possibility to have data deleted or delivered does not apply if the data is anonymized. This possibility is also limited if the data is included in completed analyses.

If you wish to withdraw from the study or have any questions concerning the study, you may contact the project leader (see information on the bottom of the page).

WHAT WILL HAPPEN TO YOUR PERSONAL INFORMATION?

Any personal data concerning health that has been recorded about you will only be used as described in the purpose of the study, and will be stored until 31.12.2040. Potential extensions of the storing of the data will only apply after approval from the ethics committee and other relevant authorities. You have the right to access information that has been recorded about you and the right to stipulate that any error(s) in the information that is recorded is/are corrected. You also have the right to know which security measures have been/will be taken when your personal data concerning health is processed.

You have the right to submit a complaint on the processing of your personal health data concerning health to the Norwegian Data Inspectorate (Datatilsynet) and the Data Protection Official (Personvernombud) at the institution.

We will align data from the questionnaires with register data from the Norwegian Patient Registry, the Norwegian Prescription Database, Dødsårsaksregisteret, Kontroll og Utbetaling av Helserefusjon and Forløpsdatabsed (FD Trygd). This is done to obtain information not assessed in the questionnaires, for example diagnosis, reason for referral and the number of prior appointments in different clinics. It will be impossible to identify you in the result of this study when they are published. All information will be processed and used

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without your name or personal identification number, or any other information that is directly identifiable to you. A code links you and your personal data concerning health via an identifier list. Only the project leader Håvard Kallestad and the head of department at St.Olavs Hospital, Østmarka will have access to this list.

Information about you will be anonymized or deleted five years after the project has ended

SHARING OF PERSONAL DATA AND TRANSFER OF PERSONAL DATA ABROAD

By agreeing to participate in the study, you are also consenting to that your information acquired through questionnaires can be transferred to another country as a part of research collaboration and publication. This can be a country where the laws do not meet the requirements of the European Data Protection Law. The project manager will therefore ensure that your personal data concerning health is kept safe. The code that connects you and your personal data concerning health will not be released. All personal data will be processed in accordance with the European Data Protection Law (GDPR).

INSURANCE

As a participant in this study you are insured through the Norwegian patient injury compensation.

APPROVAL

The Regional Committee for Medical and Health Research Ethics has reviewed and approved the Research Project, REK Sør-Øst B 125068.

In accordance with the General Data Protection Regulation the controller St. Olavs Hospital and the project manager Håvard Kallestad is independently responsible to ensure that the processing of your personal data concerning health has a legal basis.

The processing of your personal data is based on your consent.

The processing of personal data is in accordance with the General Data Protection Regulation art. 6 e and art 9 number 2 j and the Norwegian “helseforskningsloven” § 9. Your consent ensures codetermination, openness, and predictability for you in this research project.

CONTACT INFORMATION

If you have any questions regarding the research project, you can get in touch with the project leader Håvard Kallestad, tlf 72823030, or the study coordinator, tlf 920 62 945, or send an email to post@sovnmestring.no.

St.Olavs Hospital is the controller for your personal data in this project, St. Olavs Hospital, Postboks 3250 Torgården, 7006 Trondheim.

You can also get in touch with the Institution’s Data Protection Officer (personvernombud) if you have any questions related to the use of your personal health data concerning health in the research project personvernombudet@stolav.no.

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Chapter A – Further explanation of what the study involves

SCHEDULE – WHAT HAPPENS AND WHEN DOES IT HAPPEN?

This is a schedule over your participation in the study including an explanation of what each time point of assessment involves and how much time it requires.

Weeks	0 weeks	1-8 weeks	9 weeks	6 months	1 year
Inclusion screener	X				
Questionnaires	X		X	X	X
Sleep diaries	X	X	X	X	X
Treatment		X			

The inclusion screener will take approximately 10 minutes to answer and will evaluate your sleep problems to ensure that the treatment in this program is suitable to you. If you are included in the study we will ask you to answer questionnaires about your work- and family situation, your sleep and health (maximum 30 minutes). You will also be asked to complete sleep diaries 10 days before the treatment, 10 days after treatment, 10 days 6 months after treatment and 10 days 1 year after treatment. If you are randomized to Group 2 you will also be asked to complete sleep diaries during the treatment (6 weeks).

Treatment: You will be randomized into one of two possible treatment groups:

- Group 1: You will get access to a web page with information about insomnia and good sleep habits. You will have access to this page in six weeks and may log in and read the content as many times as you wish in this period. There are no specific requirements beyond this.

- Group 2: You will get access to an interactive treatment program via the internet. This program is designed to give you individually adjusted instruction about how to improve your sleep. The treatment will last for 6 weeks. You will receive weekly assignments to complete and you will be asked to complete sleep diaries via the internet every day. This will require 1 – 2 hours of your time every week.

POTENTIAL ADVANTAGES, DISADVANTAGES AND ADVERSE EVENTS

The treatment being used in this study have been tested in several studies in Norway and other countries. The results have shown that those who use this treatment achieves a lasting improvement of their sleep and daytime functioning (less sleepiness and improved mood). An advantage of participating in the study is therefore that your sleep may be improved and that you may experience less sleepiness and improved mood in the daytime.

One part of the treatment involves completing assignments aimed to change your sleep habits. This requires effort and time as described above. Some may experience this as challenging.

If you are randomized to Group 2 you may be asked in the start of the treatment to reduce the time you spend in bed. This can result in less sleep and increased daytime sleepiness in the start of the treatment. This will be a transitory period and is an important step towards improving your sleep.

If you experience a worsening of your condition during the treatment you can contact the acute ambulatory team or the health professional at the DPS where you receive your health services. These will

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evaluate and ensure that you receive the necessary treatment. This follow-up and treatment are independent of the participation in this study, but we will receive information from the team if the follow-up suggest that the event is associated with your participation in the study.

OTHER CIRCUMSTANCES

If new information becomes available that might influence your willingness to participate in the study, we commit ourselves to inform you as soon as possible. We wish that you inform us if there are circumstances that may influence your qualification in the study. This may for example be if you start working night shifts. We also wish that you inform us if you for any reason want to end your participation in the study earlier than planned.

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I CONSENT TO PARTICIPATING IN THE RESEARCH PROJECT AND THAT MY PERSONAL DATA CONCERNING HEALTH AND BIOLOGICAL MATERIAL CAN BE USED AS DESCRIBED AS ABOVE

City/Town, date

Participant's Signature

Participant's Name (in BLOCK LETTERS)

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-24+suppl.1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Suppl. 1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

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Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4-6
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7

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Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6, Fig. 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7, suppl. 2
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8

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Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-12, suppl. 3
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	14

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		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9, 11
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13-14
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	14
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7, 13-14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17

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Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	9
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	13, suppl. 4
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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