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Chronotherapy for patients with a depressive episode treated in a public outpatient mental healthcare clinic in Norway: protocol for a randomised controlled trial

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ABSTRACT

Introduction Depression is highly prevalent in outpatients receiving treatment for mental disorders. Treatment as usual (TAU) usually consists of either psychotherapy and/or antidepressant medication and often takes several weeks before clinical effect. Chronotherapy, consisting of sleep deprivation, sleep-wake phase advancement and stabilisation, and light therapy, is a possible addition to TAU that may decrease the time to treatment response. This randomised controlled trial will examine the benefits of adding chronotherapy to TAU compared with TAU alone.

Methods and analysis The trial will include 76 participants with a depressive episode who initiate outpatient treatment at a secondary mental healthcare outpatient clinic at St. Olavs University Hospital. Participants will be randomly allocated 1:1 to either chronotherapy in addition to TAU or TAU alone. Assessments will be performed at baseline, day 3, day 4, day 7, day 14 and weeks 4, 8, 24 and 52, in addition to longer-term follow ups. The main outcome is difference in levels of depressive symptoms after week 1 using the Inventory of Depressive Symptomatology Self-Report. Secondary outcomes include levels of depressive symptoms at other time points, as well as anxiety, health-related quality of life and sleep assessed through subjective and objective measures.

Ethics and dissemination The study protocol has been approved by the Regional Committee for Medical Research Ethics Central Norway (ref: 480812) and preregistered at ClinicalTrials.gov (ref: NCT05691647). Results will be published via peer-reviewed publications, presentations at research conferences and presentations for clinicians and other relevant groups. The main outcomes will be provided separately from exploratory analysis.

Trial registration number NCT05691647.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Implementation of a potentially rapid and highly potent, non-pharmacological intervention that may reduce the time to response to treatment for a major group of patients with moderate or severe depression in secondary mental healthcare.
⇒ A trial with broad eligibility criteria increases the likelihood of findings that are generalisable to other clinical settings.
⇒ Sample size allows for the detection of moderate to large effect size differences between the two groups.
⇒ Limitations include the lack of an attention control group, and translating the findings to acutely ill psychiatric populations since the sample will comprise non-urgent patient referrals.
⇒ The nature of the interventions means masking the interventions to the investigators and participants is impossible, increasing the risk of bias.

INTRODUCTION

Depression is one of the most common mental disorders with a large impact on the individual and society.[1] It is one of the most common reasons for referrals to secondary mental healthcare outpatient services in Norway, and about 30% of the patients have been diagnosed with a depressive episode.[2] It often takes several weeks before any treatment for a depressive episode has a clinically meaningful effect. This is true for both antidepressive medication[3] and psychotherapeutic treatments, for example, cognitive–behavioural therapy.[4] Thus, a major unresolved challenge is to reduce symptom severity for outpatients in a depressive episode quickly.

Chronotherapy might be a potential solution to this challenge. Chronotherapeutic interventions act on the circadian system to achieve a rapid-onset therapeutic effect[5] and include interventions such as total sleep deprivation (TSD), sleep-wake phase advancement (SPA) and stabilisation, and morning bright light therapy (BLT). Since the 1950s, it has

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repeatedly been shown that one night of TSD is associated with large and immediate reductions in depressive symptoms.[6 7] The effect occurs gradually during wakefulness and peaks after about 30–35 hours when about 50% of patients achieve remission from depressive symptoms. However, after 35 hours, the effect diminishes, and a challenge has been that patients typically experience a complete relapse after sleep.[6] Thus, TSD has had limited clinical usefulness, and methods to prolong the effect of TSD have been proposed. Of these, adding other chronotherapeutic interventions such as 3 days of SPA and sleep-wake phase stabilisation following TSD and concurrent use of BLT have been used in outpatient settings, often referred to as triple chronotherapy (TCT). In inpatient settings, the use of three nights of TSD within a week, in addition to sleep-wake phase stabilisation and BLT has also been studied as a 'TCT'.[8] However, TCT with a single night of TSD, followed by SPA and sleep-wake phase stabilisation and BLT, may arguably be more feasible for outpatient use[7] and trials support its feasibility in these settings,[9 10] though most trials of chronotherapy have been performed in inpatients.[8 11]

Two systematic reviews have shown promising results in uncontrolled trials of TCT in patients with both unipolar and bipolar depressive episodes but little data from randomised controlled trials (RCTs) are available.[7 11] Three RCTs have been performed with outpatient TCT on patients in a depressive episode. Wu *et al*[12] randomly allocated 49 outpatients with bipolar depression to TCT or medication and found that TCT yielded significantly better results both immediately after the SPA and at 7 weeks follow-up. Another trial of 44 unipolar depressed outpatients randomly allocated to TCT or an alternative protocol with fixed bedtimes and bright light without blue-green frequencies, failed to find significant differences after 1 week.[9] However, there is a possibility that this trial was slightly underpowered as there were numerical tendencies towards TCT, and another trial of 82 unipolar depress participants from primary care in the UK, found significant differences between TCT and a control condition both after 1 week and at some of the longer-term assessments.[10] There is also a lack of data that describes other potential effects of TCT, such as changes in sleep and health-related quality of life.[8] A recent meta-analysis also points out that few studies have assessed the intervention expectations of the participants before the interventions.[11]

Given the promising results, but conflicting and limited evidence from RCTs, there is a need for more RCTs of TCT in outpatient settings to further test its effectiveness, both short term (the first week after baseline), medium term (2–8 weeks after baseline) and longer term (24 and 52 weeks after baseline). We will, therefore, perform an RCT of TCT in outpatients with a moderate or severe depressive episode. To address if TCT can be included in a clinical setting, the trial is designed to test if adding TCT to treatment as usual (TAU) early in the treatment of depression in a secondary mental healthcare outpatient clinic has short-term, medium-term and longer-term effects compared with TAU alone.

Although large heterogeneity poses a major challenge for using TAU as a control condition,[13] it has been argued that TAU, as given in the community or the clinic by experienced clinicians, is one of the best control conditions in trials of psychological treatments.[14] Network meta-analyses indicate that the effect size estimates of TAU are comparable to that of placebo conditions in the treatment of depression.[15 16] As such, TAU can be regarded as an adequate control condition controlling for placebo effects.

The main aim of the trial is to test the short-term effectiveness on depressive symptoms. The main outcome will be the between-group difference in self-reported levels of depressive symptoms at 1 week after baseline.

Secondary aims are exploratory and include short-term, medium-term and long-term effectiveness of TCT on improvements of the sleep-wake cycle, insomnia severity, anxiety, quality of life, work and resource use, and medium-term and long-term effectiveness on depressive symptoms and per protocol analyses. Moreover, secondary aims are to test the effectiveness of TCT in changing short-term and medium-term objective sleep and daytime activity patterns, and adverse effects. Other exploratory secondary aims are to test if there are baseline characteristics that predict outcomes, potential mediators of outcomes and long-term effects.

METHODS AND ANALYSIS

This protocol for the RCT follows the SPIRIT statement guidelines (Standard Protocol Items for Randomised Trials) and is preregistered with ClinicalTrials.gov (identifier: NCT05691647). Figure 1 shows the flow chart for recruitment and assessments. A completed SPIRIT checklist can be found in online supplemental file 2, and a completed WHO Trial Registration Data Set can be found in online supplemental file 3.

Trial design

This will be a parallel-group, superiority RCT of 76 outpatients diagnosed with a depressive episode, allocated 1:1 to either TCT in addition to TAU or TAU alone. Assessments will be undertaken at baseline, at days 3, 4, 7 and 14, and at weeks 4, 8, 24 and 52 and later.

Recruitment and eligibility

Participants will be outpatients recruited from secondary healthcare services in the clinic of mental healthcare, St. Olavs University Hospital, Trondheim, Norway. The clinic of mental healthcare is a part of the Norwegian public healthcare system, wherein patients are referred by their general practitioners or other healthcare services. Patients with moderate to severe depression are entitled to outpatient treatment in secondary healthcare. Patients experiencing intermittent suicidal crises are typically admitted to inpatient treatment.

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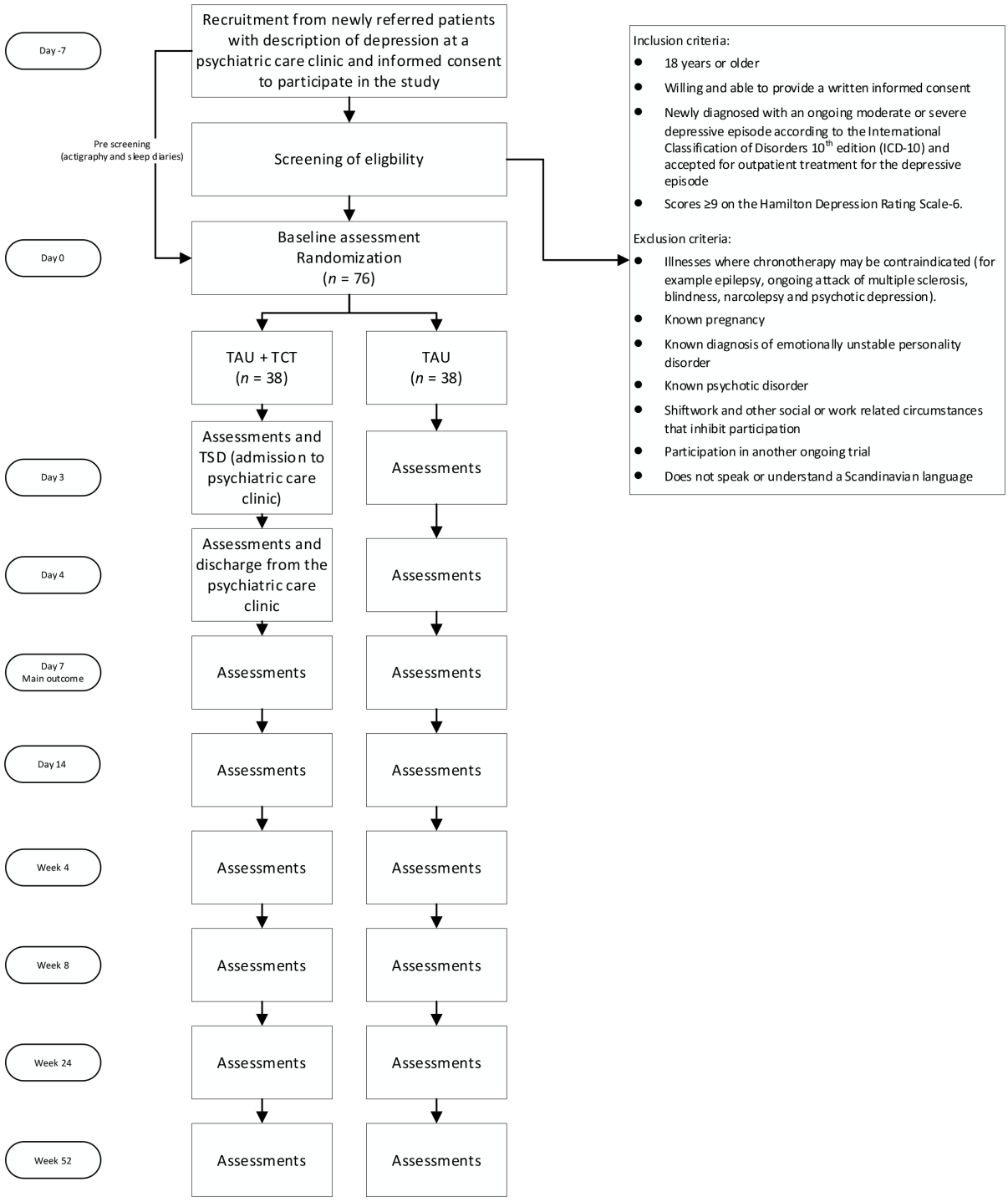

Figure 1 Flow chart. TAU; treatment as usual; TCT, triple chronotherapy; TSD; total sleep deprivation.

Newly referred patients diagnosed with a depressive episode will be eligible for the study if they comply with all the following at randomisation: (1) 18 years or older; (2) willing and able to provide a written informed consent; (3) newly diagnosed with an ongoing moderate or severe depressive episode according to the ICD-10 and accepted for outpatient treatment for the depressive episode and (4) a score ≥9 on the Hamilton Depression Rating Scale-6 (HDRS-6). Patients are considered ineligible for participation if any of the following are present: (1) illnesses where chronotherapy may be contraindicated (eg, epilepsy, ongoing attack of multiple sclerosis, blindness, narcolepsy and psychotic depression); (2) known pregnancy; (3) a known diagnosis of emotionally unstable personality disorder; (4) a known psychotic disorder; (5) shiftwork or other related social or work circumstances that inhibit participation; (6) participation in another ongoing trial or (7) does not speak or understand a Scandinavian language. The trial will recruit participants until the final sample of 76 participants is included.

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Table 1 The triple chronotherapy plan

Study day	Type of chronotherapy	Time of day
Day 0	Total sleep deprivation	Starting 07:00: The patient is awake for 34 hours
Day 1	Sleep-wake phase advancement Light therapy	Sleep opportunity: 17:00–01:00 Light therapy: 07:15–07:45
Day 2	Sleep-wake phase advancement Light therapy	Sleep opportunity: 19:00–03:00 Light therapy: 07:15–07:45
Day 3	Sleep-wake phase advancement Light therapy	Sleep opportunity: 21:00–05:00 Light therapy: 07:15–07:45
Day 4	Sleep-wake phase advancement Light therapy	Sleep opportunity: 23:00–07:00 Light therapy: 07:15–07:45
Day 5 week 8	Sleep-wake phase stabilisation Light therapy	Sleep opportunity: 23:00–07:00 Light therapy: 07:15–07:45

Interventions

Treatment as usual

Participants allocated to receive TAU alone will receive standard psychological and psychopharmacological treatment for a depressive episode at the outpatient clinic. The TAU will be provided by therapists independent of the study and the study will not influence how the responsible therapist should perform TAU. Typical interventions administered in therapy for a depressive episode include medication, cognitive–behavioural therapy and other psychotherapies. The therapists of TAU in both interventions will consist of qualified clinicians, such as clinical psychologists, psychiatrists and psychiatric nurses, who are employed at the outpatient clinic. To ensure a comprehensive approach, all cases will be thoroughly examined and discussed in interdisciplinary team meetings.

TCT and TAU

TCT involves three different interventions: A single night of TSD, 4-day SPA and stabilisation, and BLT. The TCT plan is shown in table 1. The participants will receive TAU with their assigned therapist at the outpatient clinic in addition to the chronotherapy intervention, which includes concomitant interventions decided by the therapist. The study will not pose restrictions or guidelines to concomitant care.

TSD/wake therapy

TSD involves the participant staying awake for 34 hours, from 07:00 to 17:00. To assist wake and ensure that the participants adhere to the TSD, they will be admitted to a one-night stay at the inpatient ward connected to the outpatient clinic at St. Olavs University Hospital. The TSD will start on day 3 after randomisation, and the participants will be admitted to the inpatient ward and discharged the following day, day 4 after randomisation.

During the night at the inpatient ward, participants will not have a room but will be offered to engage in activities in the common areas. There will be available night staff at the ward. If participants fall asleep, they will be woken up by the staff. Staff will register deviations from the protocol. Before discharge, the study team will meet the participants to plan how to stay awake the following day and conduct assessments. The participants will be encouraged to attend work if employed. However, they will receive a letter that describes that they are participating in a study that may contribute to impaired cognitive function and increased fatigue that they can choose to give their employer. If employed in an occupation that requires alertness and cognitive functioning, such as a professional driver, sick leave will be given for the first day after sleep deprivation. They will receive psychoeducation and printed information about common symptoms and their sleep schedule for the following days to compensate for possible cognitive problems and to increase adherence. The participants are scheduled to go to bed at 17:00 on the day they are discharged. See table 1 for an overview of the sleep schedule participants are asked to adhere to.

SPA and stabilisation

On discharge, participants are encouraged to adhere to the sleep schedule. For study day 4, participants should go to sleep at 17:00 and rise at 01:00. For the following nights, the sleep period is advanced by 2 hours (19:00–03:00; 21:00–05:00; 23:00–07:00). The study team will have daily contact with the participants during the SPA to encourage participants to adhere to treatment, to support participants, and to answer possible questions and worries the participants may encounter. On study day 7, participants will be contacted by the study team to assess symptoms after TSD and the SPA. After the SPA, participants will start the sleep-wake stabilisation. This involves the patient to adhere to a sleep period between 23:00 and 07:00.

Light therapy: From day 4 in the study flow, the participants will be exposed to BLT every day from 07:15 to 07:45 for 8 weeks. The BLT is performed with the light box Lumie Brazil (Lumie), which is tested to produce 10 000 lux white light at a 35 cm distance. Participants will receive printed information with instructions for the use

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of the light box, including time points and the distance to place the light box from the body (30 min at 35 cm distance).

Randomisation

Sequence generation, implementation and allocation concealment mechanism

Included participants will be randomised to TCT plus TAU or TAU alone by a web-based system developed and administered by the Unit of Applied Clinical Research, Norwegian University of Science and Technology and St. Olavs University Hospital, Trondheim, Norway. Participants will be randomised 1:1 using block randomisation with a random block size. The study team cannot influence the randomisation process in any way. The study team and participants will be made aware of the participants' assigned condition after baseline assessments are completed on day 0 in the study flow. This will allow the participants allocated to TCT plus TAU to plan the logistics regarding one night of admission to the secondary mental healthcare inpatient psychiatric unit.

Awareness of assignment

Masking will not be applicable due to the nature of the study, in which participants randomised to receive chronotherapy plus TAU will be admitted to the ward for a one-night sleep deprivation, and the participants and researchers will understand which intervention arm the participant is receiving. Analyses will be conducted by a statistician who is blinded to intervention allocation.

Withdrawal

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

Modifications of interventions

Unexpected medical situations may lead to a modification of allocated intervention. For example, the occurrence of a psychotic episode and the presence of an imminent suicidal risk for an included and randomised participant may require the participant to be admitted to an inpatient treatment facility, consequently impacting the originally designated outpatient treatment plan.

Crisis management procedure

All participants will have access to emergency medical care via the regular Norwegian healthcare system in the event of adverse events. Serious adverse events for the first 14 days of the intervention will be reported continuously to the investigators.

Assessments

Diagnostic assessments will be made using a structured clinical diagnostic interview (SCID-KV or M.I.N.I plus according to the clinic strategy).[17 18] The main outcome is a change in the severity of depressive symptoms measured by the Inventory of Depressive Symptomatology-Self Report (IDS-SR)[19] from baseline to week 1 after randomisation. Other measures relate to secondary outcomes. Descriptions of all measures used in the study will be provided below. Online supplemental table 1 summarises the timing of each of the assessments.

Demographic data and background variables: Key demographic data will be collected at baseline, including age, gender, education level, cohabitation status, number of children living at home and known somatic illness. Background information includes secondary diagnoses, number of previous depressive episodes and estimates of the length of previous depressive episodes, functional decline in these episodes and the age of first depressive episode onset given both from the patients and from their hospital records.

Primary outcome measure

IDS-SR:[19] The IDS-SR is a self-report questionnaire that measures depressive symptoms over the past 7 days. The 30 items are rated on a Likert scale from 0 to 3, with higher scores indicating more depressive symptoms. The total scores are based on 30 items; the range is 0–84. The questionnaire will be applied with 30 items for all assessment points except for day 4, in which sleep items (items #2, #3, #4) are removed. On days 3, 4 and 7, the questionnaire will ask for depressive symptoms over the past 24 hours. The Norwegian version is licensed by Mapi Research Trust.

Other measures of depression and anxiety

HDRS-6:[20 21] The HDRS-6 is an observer-rated questionnaire that measures depressive symptoms with good psychometric properties.[22] Items are rated on a Likert scale from 0 to 4, with a total range of 0–22, where a higher score indicates more depressive symptoms. Scores of ≥9 are classified as moderate or more severe symptoms. HDRS-6 has been translated from English to Norwegian by an expert committee.

Suicidality will be assessed through an item derived from the HDRS-17.[21] The item asks for suicidal ideation over the past 24 hours and is scored on a Likert scale from 0 to 4.

General Anxiety Disorder-7 (GAD-7):[23 24] The GAD-7 is a self-administered questionnaire that measures central symptoms of anxiety the past 2 weeks. The seven items are scored on a Likert scale from 0 to 3, with a higher score indicating more anxiety, giving a total range from 0 to 21. Scores 5–9 indicate mild anxiety; scores 10–14 indicate moderate anxiety and 15–21 indicate severe anxiety.[23]

Sleep measures

Insomnia Severity Index (ISI):[25 26] The ISI is a self-administered questionnaire that measures the participants' overall insomnia severity over the past 2 weeks. The seven items are scored on a Likert scale from 0 to 4, with a higher score indicating greater insomnia severity; the total range is 0 to 28.

Consensus sleep diary:[27] Sleep diaries provide subjective, daily estimates of sleep-wake periods. In addition,

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the sleep diaries have items that assess daily mood variation and whether the individual has used the light box. The sleep diaries will be used to derive information about adherence to the treatment plan, assess sleep parameters and assess daily variation in mood. Participants will fill out sleep diaries for seven consecutive days before randomisation, during the first phase of the intervention and for each follow-up assessment.

Brief Horne-Östberg Morningness-Eveningness Questionnaire (MEQ):[28 29] The MEQ is a self-administered questionnaire that measures chronotype. The brief 5-item version composites a total score range from 4 to 25, with lower scores indicating a greater preference for eveningness.

Health and somatic symptoms

EQ-5D-5L:[30 31] The EQ-5D-5L is a self-administered questionnaire that assesses general health and health-related quality of life on the measurement day. The five items are rated on a 5-point Likert scale in addition to a 0–100 rating of overall experienced health condition and allows measurement of quality-adjusted life-years.

Karolinska Sleepiness Scale (KSS):[32] The KSS is a self-report measure that assesses subjective sleepiness. The nine items are scored on a Likert scale every second hour from 1 (extremely alert) to 9 (extremely sleepy-fighting sleep) throughout the night. The questionnaire will only be given to the intervention group to assess their sleepiness during the 34 hours of sleep deprivation. There exists no validation of the Norwegian version of the KSS.

Intervention-related assessments

Stanford Expectations of Treatment Scale (SETS):[33] The SETS is a self-report measure that assesses patients' negative and positive expectations of interventions. It contains six items rated on a Likert scale from 1 (strongly disagree) to 7 (strongly agree) and will be assessed at baseline for all participants. SETS is translated and back-translated to Norwegian.[34]

Patient satisfaction and experienced adverse effects: A self-report measure was developed to assess the participants' subjective experiences in the study. The measure includes items to assess whether the interventions have positive and negative effects. It will consist of a free-text space to elaborate if none of the expected effects are experienced, and how clinical implementation can be improved.

Adverse events. Adverse events will be reported to the clinic continuously. All included patients in the intervention and control group are under weekly or biweekly contact with their therapist and can contact the clinic outside of scheduled appointments.

Work and resource use assessments

Work and Social Adjustment Scale (WSAS):[35 36] The WSAS is a self-administered questionnaire that measures the subjective experience of functionality in work and social environments. The five items are rated on an 8-point Likert scale. Total scores range from 0 to 40, with a higher score indicating more functional impairment.

Use of healthcare services and function in work: Number of outpatient contacts, number of admittances as inpatients and days admitted will be recorded, and working activity, both based on self-report and hospital registries. Long-term effects from the interventions will be assessed after 5 and 10 years and possibly later through questionnaires, national registries and hospital records for explorative analyses.

Activity assessment

Actigraphy: Actigraphs are hand-worn activity sensors that provide an overall summary of activity and sleep patterns. Actigraphy data will be collected with GENEActive actiwatches to derive information about adherence to the treatment plan and to objectively assess the sleep-wake phase and other sleep and activity measures and will provide information about chronotype throughout the study. Participants will use actiwatches for seven consecutive days before the intervention starts, during the first phase of the intervention and for each follow-up assessment.

Administration of assessments

The assessment of HDRS-6 at baseline will be conducted face to face. Assessments at later time points will be administered through electronic self-report and face-to-face assessments or video consultations online to assess HDRS-6. The study team will remind all participants of the assessment time point through telephone calls, text messages and emails.

Sample size

The primary outcome is the between-group difference in IDS-SR scores 1 week after randomisation, with additional outcomes assessed on days 3, 4, 14 and weeks 4, 8, 24 and 52 weeks after randomisation.

A meta-analysis of four RCTs of sleep deprivation for depression found a standardised effect size (ES) of Hedges g=0.62.[11] In a feasibility trial of TCT in a primary care sample, the authors reported a mean effect size of d=0.89 on the QIDS-SR at 1 week.[10] We anticipate that 25% of participants in our sample will not complete the follow-up assessments and that the between-group effect of TCT will be somewhat lower than Veale *et al*[10] reported due to differences in design and sample. Therefore, we aim to recruit 76 participants to retain 60 participants (30 in each treatment arm) at the end of the week 1 assessment. For a two-sample t-test with alpha=0.05, a sample size of 60 participants will provide an 80% chance of detecting a between-group difference of Cohen's d=0.75. This corresponds to a moderate-large effect size difference between the two groups and is considered clinically meaningful.

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Statistical analytical plan

We will use intention-to-treat analyses for all outcomes. Per-protocol analyses will additionally be performed for individuals who complete the interventions.

We plan to use linear mixed model analysis to examine the difference between the two randomised groups on the primary and secondary outcomes with continuous variables. Time as categorical covariate and treatment group and their interaction are the main covariates. We will omit a systematic main effect of treatment at baseline (before randomisation) and in this way adjust for baseline as recommended by Coffman *et al* and[37] Twisk *et al*.[38] This is termed constrained analysis by Coffman *et al*.[37] The patient is included as a random effect. Normality of residuals will be checked by inspecting QQ-plots. Possible deviations will be handled using bootstrapping or other appropriate methods. Secondary analyses with dichotomous outcome variables will be handled similarly using logistic mixed models.

Linear mixed models include all participants in the analysis, also those with missing data at one or more time points. The results are unbiased under the missing at random (MAR) assumption, while a complete-case analysis would be unbiased only under the more restrictive missing completely at random assumption. Similarly, logistic mixed models provide approximately unbiased results under the MAR assumption.

Two-sided p values under 0.05 are considered statistically significant, and we report 95% CIs where relevant.

Patient and public involvement

The service user group for mental healthcare at the Central Norwegian Health Trust was consulted in the planning of the study design and has provided feedback on the assessments and timing of these included in the protocol.

Ethics and dissemination

The trial protocol has been approved by the Regional Committee for Medical Research Ethics Central Norway (ref: 480812) and is preregistered at ClinicalTrials.gov (ref: NCT05691647). The trial follows the guidance and principles outlined in the Revised Declaration of Geneva.[39] Before study entry, eligible individuals provide a written informed consent, see online supplemental files 4; 5. The level of care and treatment at the mental health clinic will remain the same regardless of study participation. The participants will be made aware of this through oral and written communication.

Data from the trial participants will be gathered using services for sensitive data (TSD) and stored in accordance with the General Data Protection Regulation. Access to data is regulated through Data Protection Impact Assessment approved by St. Olavs University Hospital.

Findings from the RCT will be presented at conferences and published in peer-reviewed scientific journals. The first academic publication will report between-group differences in depressive symptoms and other self-reported outcomes. Subsequent publications will include secondary analyses of outcomes measures and discoveries about feasibility. In addition, the patient user group and the outpatient clinic staff will be presented with the results. The investigators will adhere to international guidelines regarding multiauthorship of manuscripts.

Study monitoring

A Data and Safety Monitoring Committee, including the project leader, project coordinator, investigators and clinical representatives, will meet weekly during the start-up phase, and then biweekly to monitor the study progress, the status of inclusion and any reports of adverse events. Statistical advisors, administrative leaders and other representatives will be co-opted when necessary. The Central Norwegian Health Trust and the trial sponsor routinely and randomly audits research projects yearly. This ensures that trial protocols are followed and that ethical standards are followed. In the case of important amendments to the trial protocol, these will first we evaluated by the ethics committee and published on relevant study websites.

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Contributors The study was designed by the research team: HK, SS, KL, GM, JØØH, LSSE, LSR, NK. HK and KL conceived of the study. LSR and NK produced the first draft of the protocol paper with input from HK, GM, SS and JØØH. SL and HK 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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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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