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Effects of E-aid cognitive behavioral therapy for insomnia (eCBTI) to prevent the transition from short-term insomnia to chronic insomnia: study protocol for a randomized controlled trial

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Keywords:	E-aid cognitive behavior therapy for insomnia, short-term insomnia disorders, randomized controlled trial

STUDY PROTOCOL

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Effects of E-aid cognitive behavioral therapy for insomnia (eCBTI) to prevent the transition from short-term insomnia to chronic insomnia: study protocol for a randomized controlled trial

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Abstract

Introduction: Previous evidence suggested that online self-guided sleep intervention is efficacious in improving treatment outcomes in patients with chronic insomnia. However, the research on online sleep interventions targeting short-term insomnia disorders (STID) has been scarce. This study aims to evaluate the feasibility and effectiveness of brief e-aid cognitive behavioral therapy for insomnia (eCBTI) in treating acute insomnia and preventing transition from short-term insomnia to chronic insomnia.

Methods and analysis: This is a pragmatic two-arm multi-center, randomized controlled trial comparing eCBTI with treatment as usual (TAU) in outpatients. Two hundred patients with STID (as defined by DSM-5) will be recruited. Patients will be randomly assigned to receive one-week eCBTI via a Smartphone application, or to receive treatment as usual. Treatment effects will be assessed at 1 week and 3 months after intervention. The primary outcome of the study, whether the eCBTI program is sufficient in preventing transition from short-term to chronic insomnia, is measured by Insomnia Severity Index (ISI). Secondary outcome measurements include Dysfunctional Beliefs and Attitudes about Sleep (DBAS), Ford Insomnia Response to Stress Test (FIRST), Sleep Hygiene and Practices Scale (SHPS), Pre-sleep Arousal Scale (PSAS), and Epworth Sleepiness Scale (ESS). Additionally, Hospital Anxiety and Depression Scale (HADS) and the Short-Form 12-Item Health Survey (SF-12) will be used for the measurement of mood symptoms and quality of life.

Discussion: This study will be the first one in China to investigate whether a brief eCBTI program is sufficient to treat acute insomnia and to prevent its transition to chronic insomnia by using a widely-used smartphone application. The findings may also help to understand the key hypothesis that STID is a contributory causal factor or a part of the natural course in the development of chronic insomnia.

Ethics and dissemination: The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). The results of the investigation will be published in scientific papers.

Trial registration: NCT03302455 (clinicaltrials.gov). Date of registration: October 5, 2017.

***Keywords*:** E-aid cognitive behavior therapy for insomnia (eCBTI), short-term insomnia disorders (STID), randomized controlled trial (RCT).

Article Summary (Strengths and limitations)

- E-aid cognitive behavior therapy for insomnia (eCBTI) is more efficient, flexible, and time-saving compared to traditional face-to-face CBTI.
- This study will investigate the feasibility and effectiveness of short-term eCBTI in treating acute insomnia and preventing transition to chronic insomnia in detail.
- Two hundred participants with Short-term Insomnia Disorders will be randomly divided into eCBTI group (1-week online core treatment) or control group (treatment as usual).
- Participants' insomnia symptoms, anxiety, depression, and quality of life will be assessed by standardized questionnaires pre- and post-intervention.
- Double-blinded study design is unable to be fulfilled in the current study, only the onsite-research staff were blinded to the group assignment.

Abbreviations

CBT, Cognitive Behavioral Therapy

CI, Confidence Intervals

CID, Chronic Insomnia Disorder

DBAS, Dysfunctional Beliefs and Attitudes about Sleep

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

eCBTI, e-aid Cognitive Behavior Therapy for Insomnia

ESS, Epworth Sleepiness Scale

FIRST, Ford Insomnia Response to Stress Test

HADS, Hospital Anxiety and Depression Scale

ISI, Insomnia Severity Index

ITT, Intention to Treat

LOCF, Last Observation Carried Forward

MEQ, Morningness-Eveningness Questionnaire

PP, Per Protocol

PSAS, Pre-sleep Arousal Scale

RCT, Randomized Controlled Trial

SF-12, Short-Form 12-Item Health Survey

SHPS, Sleep Hygiene and Practices Scale

STID, Short-term Insomnia Disorders

TAS, Treatment Adherence Scale

TAU, Treatment as Usual

TSS, Treatment Satisfaction Scale

WMP, WeChat Mini Program

Background

Insomnia disorder

Insomnia is one of the most common sleep disorders. Most studies reported that 10-15% of adults meet the clinical diagnostic criteria for insomnia disorder [1]. On average, The economic burden of insomnia is 5010 US dollars per person per year, comparing with 421 dollars per year in an individual with good sleep [2]. In addition, indirect consequential impairment caused by insomnia (such as work-related injuries and sickness leave) is significantly greater than direct damage (such as cost of treatment of insomnia). Moreover, insomnia is a prodromal symptom and risk factor for the development and persistence of various physical and mental disorders [3, 4].

Based upon the course of illness, Insomnia is classified as chronic insomnia disorder (CID) (> three months) or short-term insomnia disorder (STID) (< 3 months) [5]. The diagnostic criteria for these two types of insomnia are similar, but CID includes a minimum frequency of 'more than three nights per week' while STID has no such criteria [5]. It is worth mentioning that STID is a common social phenomenon, and most people would have experienced it, especially in response to situational stress or rapid changes in circadian rhythm [6]. STID is often considered as a normal bio-psychological response with no significant impairment, STID attracts less research attention than chronic insomnia [7]. Few longitudinal studies have investigated the natural course of insomnia. In the only two prospective studies conducted by Elis et al. specifically focusing on STID, the annual prevalence of STID was reported to be 36% and about 40% of the STID patients eventually developed chronic insomnia disorder [8, 9]. These two studies showed a high prevalence of STID and a high susceptibility of developing long-term insomnia in those with STID, which indicated that STID could be a key transitional stage in the course of chronic insomnia. The findings suggested a need for developing timely, active intervention to prevent the conversion of STID into chronic insomnia.

Whilst sleep disturbances may gradually improve in some patients once the initial stressors are resolved, a portion of patients with STID may eventually transit to developing chronic insomnia despite the resolution of the environmental stressors [5, 10]. Due to the high recurrence rate of

short-term insomnia, patients with STID need to be actively treated. Furthermore, early psycho-behavioral interventions and/or medication are important to prevent short-term insomnia from the transition to chronic insomnia.

Cognitive behavioral therapy for insomnia (CBTI)

Currently, treatment for insomnia includes psycho-behavioral intervention and/or medication. The psycho-behavioral therapy mostly refers to Cognitive Behavioral Therapy for Insomnia (CBTI), which is a treatment approach for insomnia with a strong evidence base [11]. CBTI aims to address the cognitive and behavioral factors that perpetuate insomnia, and consists of a constellation of treatment components, such as sleep hygiene education, relaxation therapy, stimulus control, sleep restriction, and cognitive therapy [12, 13]. In addition, CBTI may increase patients' self-efficacy and confidence to control their sleep problems and is currently suggested as the first-line treatment of insomnia in adults [14]. However, traditional CBTI program mainly focuses on the maintenance factors of insomnia, thus, it is mostly applied to treat chronic insomnia disorder [14]. A study with small sample size (n=40) by Ellis et al. showed that brief version of CBTI is effective as the treatment of acute insomnia [15]. However, little is known about whether CBTI can prevent the transition of STID to CID. In addition, the dissemination of CBTI may be limited due to several obstacles. For example, the treatment procedure is complex, time-consuming, and costly [16]. It typically requires patients to travel to the hospital/clinic for face-to-face treatment, which may interfere with patients' routine work. In addition, CBTI is a specialized treatment approach which should be conducted by trained therapists, there may be significant variations between different therapists and clinical settings. Without proper guidance at home, patients may not be able to effectively apply the treatment strategies (e.g. relaxation, stimulus control, sleep restriction), which in turn might hinder the resolution of insomnia. Additionally, CBTI requires patients to record their sleep pattern every night. This task might increase patient's anxiety and aggravate their insomnia symptoms. To address these challenges, internet-based CBTI has been developed and has been receiving widespread attention in the recent years, as it makes the delivery of CBTI more efficient and flexible, and helps to overcome the above shortcomings often associated with face-to-face treatment modality [17-19]. Several e-aid CBTI (eCBTI) treatment tools have been made available in the

western countries (e.g. Sleepio, SHUTi), and have shown similar efficacy as compared to standard CBTI [18, 20-23]. However, further exploration and verification are still needed to examine the efficacy of eCBTI as a treatment for STID in Chinese population.

The current study

In this study, we plan to establish a short-term eCBTI treatment program in Chinese to test whether eCBTI can reduce the transition from STID to chronic insomnia disorder. Moreover, we aim to investigate whether this program can improve sleep, anxiety, depression, and quality of life in individuals with STID.

The primary hypothesis for the trial is:

The eCBTI intervention can reduce transition of STID to CID;

The secondary hypotheses are:

1. The eCBTI intervention can improve sleep in patients with STID.
2. The eCBTI intervention can improve depressive and anxiety symptoms in patients with STID;
3. The eCBTI intervention can improve patients' overall health status and quality of life.

Methods/Design

Research design

This study is a parallel assignment, randomized controlled trial to compare eCBTI intervention versus treatment as usual (TAU). The screening, assessments, allocation, and intervention will all be carried out via a WeChat Mini Program (WMP) specially tailored for the trial. An information sheet will be provided online, and informed consent will be completed online before participation in the study. The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). The research design is summarized in Fig. 1.

Participants

We plan to recruit 200 participants diagnosed with STID according to the sample size estimation. Participants will be recruited from sleep clinics in 31 hospital sites in mainland China, and will be randomly allocated to two groups, namely, eCBTI or control group (TAU). The eCBTI group will receive eCBTI core treatment daily for 1 week in addition to TAU, while the control group will only receive TAU.

Eligibility criteria

To be included, participants must fulfill the following inclusion criteria:

A. Meeting the diagnostic criteria for short-term insomnia disorder according to DSM-5,

B. 18 years of age or older,

C. being able to comply to the intervention,

D. Provision of electronic informed consent,

E. Own and know how to use smart gadgets (such as smartphones, tablets, and computers).

Participants will be excluded if they meet the following exclusion criteria:

A. Having a diagnosis of a significant untreated mental or medical illness (e.g. consciousness disturbances, mania, acute phase of schizophrenia, major depressive disorder, etc.),

B. Have been receiving any kind of psychological treatment for insomnia in the past 6 months,

C. Shift workers, frequent night shift workers, frequent cross-time fliers (e.g. international flight crew, shifted nurse/health professionals),

To allow for greater generalizability, this study does not exclude patients with a stable condition of somatic disease, mental disorders (e.g. depression in remission), and sleep disorders, or individuals receiving pharmacological treatments (e.g. antihypertensive drugs, antidepressants, and benzodiazepines).

Randomization

This study is a randomized controlled trial. Participants fulfilling the study criteria will be randomly allocated to either eCBTI or Control group using simple randomization [24]. An independent researcher will implement randomization and treatment allocation, which will be conducted through an online system.

Blinding

Onsite-research staff will be blinded to the group assignment. The researcher who carries out the randomization procedure will be blinded to the study protocol.

Assessment points

Assessments will be conducted at week 0 (baseline), week 2 (one week post treatment), and week 12 (3-month after intervention). In consideration of ethical matters, participants in the control group will be offered eCBTI at week 12.

Planned intervention

After baseline assessment, participants will be randomly assigned to receive one-week eCBTI or to receive treatment as usual. E-CBTI will be delivered using the WeChat Mini Program. The program and all tools can be accessed using the WeChat app of any smartphone. Participants in the eCBTI group will receive the core sessions daily for one week. Participants will be provided with individualized treatment with the behavioral components (e.g. stimulus control, sleep restriction) according to their sleep pattern in the past 2 weeks prior to the treatment session), as well as the cognitive components (e.g. cognitive restructuring, paradoxical intention). Treatment elements also include daily sleep diary, relaxation audios (e.g. body scan, breathing exercise), and sleep hygiene education. The treatment content is designed based on the guidelines for CBTI [12, 25, 26].

Assessment of safety

CBTI is a cognitive behavioral therapy and its risk of severe adverse events is low. Previous studies indicated that online CBTI is rather safe and did not report any adverse outcomes [27]. In the current study, participant's insomnia severity will be monitored by subjective measurements during treatment and at a 3-month follow up. Participants will be allowed to attend their usual clinical follow-up in the clinic and concurrently receive routine treatments for their clinical conditions, where needed. Any participant who reports worse insomnia symptoms after the completion of intervention will be introduced to receive standard treatment for insomnia (medication and/or non-pharmaceutical treatment).

Outcome measures

Participants will receive a WeChat notification to complete the assessments online. At all times, all the assessment will be consistent across participants. If participants do not complete the questionnaire within two days, they will receive a reminder message. At baseline, demographics and related clinical data will be collected. Descriptive data on lifestyle practices such as tea and coffee consumption, smoking, and alcohol use will also be recorded.

Primary outcome measures

The Change in insomnia symptoms will be measured by the insomnia severity index (ISI) [28, 29], which assesses the severity, nature, and impact of insomnia. It is a 7-item self-report measure, ranging from 0 (no problem) to 4 (very severe problem). The resulting sum score of the ISI ranges from 0 to 28. This outcome will be measured again at week 2 (one week after treatment is complete) and week 12 (three month follow-up) in both eCBTI and Control groups.

Another primary outcome measure is the Ford Insomnia Response to Stress Test (FIRST) [30], a measure to identify sleep disturbance and predisposition to chronic insomnia. Scores on this nine-item self-report questionnaire range from 9 to 36.

Secondary outcome measures

Subjects' general sleep hygiene and practices will be measured with Sleep Hygiene and Practices Scale (SHPS) [31]. Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS) [32] will be used to measure sleep-related beliefs, potential treatments, expectations, and attitudes

towards causes. Problems of sleep initiation will be assessed with the Pre-Sleep Arousal Scale (PSAS) [33]. We will also assess patient's chronotype using the 5-item Morningness-Eveningness Questionnaire (MEQ-5) [34], generic health outcomes from the patient's perspective using the 12-Item Short Form Health Survey(SF-12) [35, 36], and anxiety and depression level using the Hospital Anxiety and Depression Scale (HADS) [37]. Participants in the treatment group will be also asked to complete a self-reported questionnaire to assess their treatment adherence and perceived helpfulness using Treatment Adherence Scale (TAS) [38]. Participants' satisfaction with the treatment will be measured using Treatment Satisfaction Scale (TSS) [39].

Sample size estimation

Previous studies have indicated that approximately 40% of STID patients transits to chronic insomnia disorders [8, 9]. Based on our previous clinical experience, we anticipate that more than 70% of the subjects will have been retained at 12-week follow-up. In order to meet the 95% confidence intervals (CI) with 35%-49% requirement, the current project needs 200 cases of short-term insomnia disorder. This sample size ensures the statistical effect is greater than 0.8 in continuous data of small sample (Cohen d = 0.30), and also ensures that the odds ratio (OR) of dichotomous variables is greater than 1.50 ($p>0.05$).

Statistical analysis

Intention to treat (ITT) [40] will be used for the main efficacy analysis and per protocol (PP) for the consistency test. ITT group consists of all participants who have undergone at least one week of treatment and evaluation. PP group refers to all ITT subjects who have not experienced significant program deviation or violation. In ITT analysis, last observation carried forward (LOCF) method will be used to analyze any missing therapeutic data.

Mean with standard deviation for continuous variables, and the frequency with a percentage for categorical variables will be reported. Independent t-test and non-parametric analyses, where appropriate, will be applied to compare the differences between two groups. Repeated measurement analysis will be utilized to compare the changes of symptoms (e.g. ISI score) following treatment and at 3-month follow-up. The clinical outcome of categorical variables will be computed using survival analysis or Chi Square test, such as the appearance of suicidal

ideation (as measured by 'Yes/No' question). Statistical analyses will be conducted using SPSS Analytics software v.22.0. Alpha will be set as 0.05 for all tests (2 sided).

Ethics and Dissemination

The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). The results of the investigation will be published in scientific papers. The data from the investigation will be made available online if necessary.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research.

Discussion

STID is a common phenomenon and might be a significant contributory causal factor in the transition from short-term insomnia to chronic insomnia. E-aid CBTI is more efficient, flexible, and time-saving compared to traditional face-to-face CBTI, and may also help to improve an individual's mood disturbance (e.g. anxiety and depressive symptoms) as well as quality of life. The main aim of the current trial is to investigate whether a brief eCBTI programme is effective to treat acute insomnia and to prevent its transition to chronic insomnia. A previous placebo-controlled RCT demonstrated that online CBTI yields an effect size comparable to that of a traditionally delivered face to face therapy [27]. Furthermore, a previous RCT has provided some preliminary support for the efficacy of treating acute insomnia with a test of single-shot CBTI [15]. The study design benefits from being administered online with a smartphone app which is used widely in China, allowing us to recruit adequate research participants and limit researcher bias during the conduct of the study. Nonetheless, the study will test the key hypothesis that STID is a contributory causal factor or natural course in the occurrence of chronic insomnia.

Trial status

Recruitment began in October 2017. It is anticipated that recruitment will be complete by October 2019, and that trial results will be available in 2020.

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Authors' contributions

BZ designed the study. All authors contributed and actively participated to the proposal. All authors endorsed the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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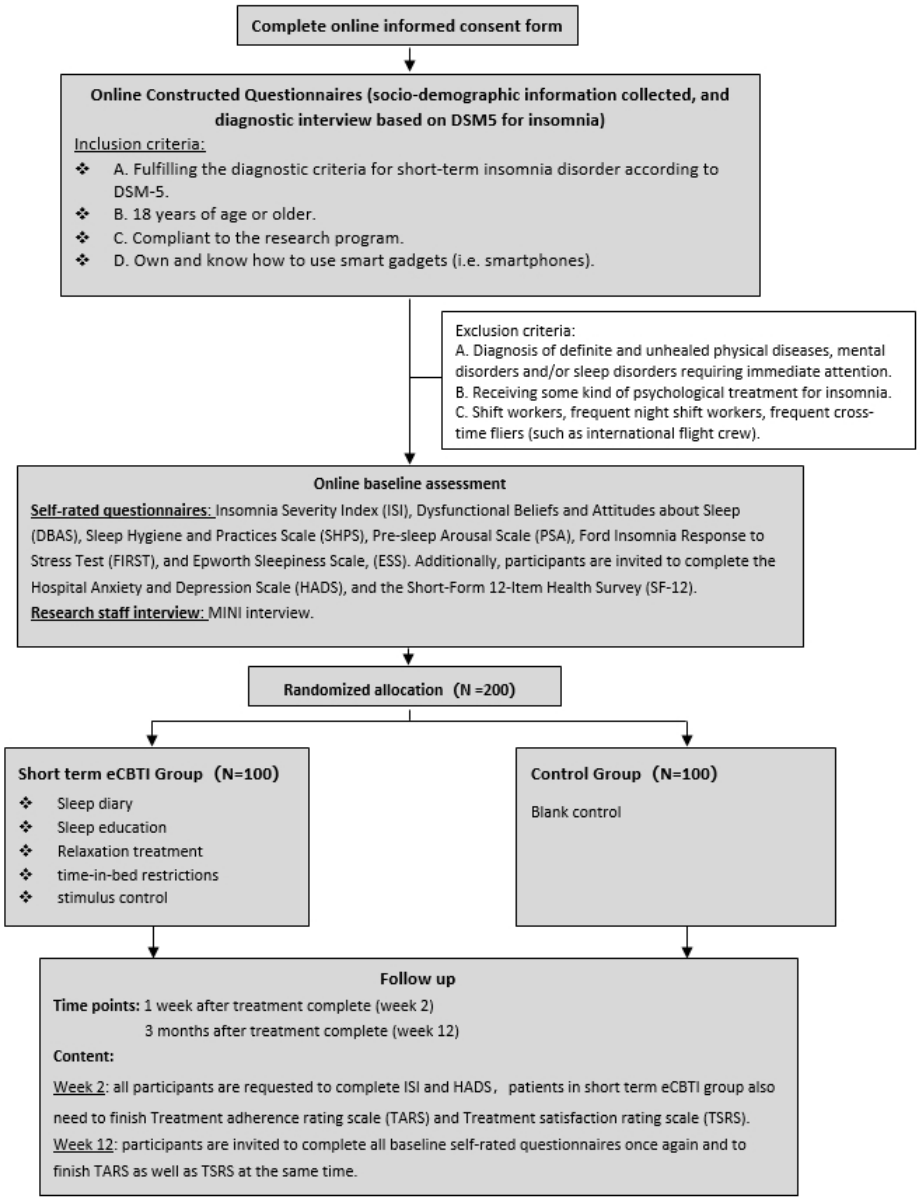
Figure legend

Figure 1 Recruitment Flowchart


Complete online informed consent form
Online Constructed Questionnaires (socio-demographic information collected, and diagnostic interview based on DSM5 for insomnia)
Inclusion criteria:
A. Fulfilling the diagnostic criteria for short-term insomnia disorder according to DSM-5.
B. 18 years of age or older.
C. Compliant to the research program.
D. Own and know how to use smart gadgets (i.e. smartphones).
Exclusion criteria:
A. Diagnosis of definite and unhealed physical diseases, mental disorders and/or sleep disorders requiring immediate attention.
B. Receiving some kind of psychological treatment for insomnia.
C. Shift workers, frequent night shift workers, frequent cross-time fliers (such as international flight crew).
Online baseline assessment
Self-rated questionnaires: Insomnia Severity Index (ISI), Dysfunctional Beliefs and Attitudes about Sleep (DBAS), Sleep Hygiene and Practices Scale (SHPS), Pre-sleep Arousal Scale (PSA), Ford Insomnia Response to Stress Test (FIRST), and Epworth Sleepiness Scale, (ESS). Additionally, participants are invited to complete the Hospital Anxiety and Depression Scale (HADS), and the Short-Form 12-Item Health Survey (SF-12).
Research staff interview: MINI interview.
Randomized allocation (N =200)
Short term eCBTI Group (N=100)
Sleep diary
Sleep education
Relaxation treatment
time-in-bed restrictions
stimulus control
Control Group (N=100)
Blank control
Follow up
Time points: 1 week after treatment complete (week 2)
3 months after treatment complete (week 12)
Content:
Week 2: all participants are requested to complete ISI and HADS, patients in short term eCBTI group also need to finish Treatment adherence rating scale (TARS) and Treatment satisfaction rating scale (TSRS).
Week 12: participants are invited to complete all baseline self-rated questionnaires once again and to finish TARS as well as TSRS at the same time.

Flowchart

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Primary Subject Heading:	Mental health
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Abstract

Introduction: Previous evidence suggested that online self-guided sleep intervention is efficacious in improving treatment outcomes in patients with persistent insomnia. However, the research on online sleep interventions targeting episodic insomnia has been scarce. This study aims to evaluate the effectiveness of brief e-aid cognitive behavioral therapy for insomnia (eCBTI) in preventing transition from episodic insomnia to persistent insomnia.

Methods and analysis: This is a pragmatic two-arm multi-center, randomized controlled trial comparing eCBTI with treatment as usual (TAU) in outpatients. Two hundred patients with episodic insomnia (as defined by DSM-5) will be recruited. Patients will be randomly assigned to receive one-week eCBTI via a Smartphone application, or to receive treatment as usual. Treatment effects will be assessed at 1 week and 3 months after intervention. The primary outcome of the study, whether the eCBTI program is sufficient in preventing transition from short-term to persistent insomnia, is measured by Insomnia Severity Index (ISI). Secondary outcome measurements include Dysfunctional Beliefs and Attitudes about Sleep (DBAS), Ford Insomnia Response to Stress Test (FIRST), Sleep Hygiene and Practices Scale (SHPS), Pre-sleep Arousal Scale (PSAS), and Epworth Sleepiness Scale (ESS). Additionally, Hospital Anxiety and Depression Scale (HADS) and the Short-Form 12-Item Health Survey (SF-12) will be used for the measurement of mood symptoms and quality of life.

Ethics and dissemination: The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). The results of the investigation will be published in scientific papers.

Trial registration: NCT03302455 (clinicaltrials.gov). Date of registration: October 5, 2017.

***Keywords*:** E-aid cognitive behavior therapy for insomnia (eCBTI), episodic insomnia, randomized controlled trial (RCT).

Article Summary (Strengths and limitations)

- This study will investigate the effectiveness of short-term eCBTI in preventing transition from episodic insomnia to persistent insomnia.
- Two hundred participants with episodic insomnia will be randomly divided into eCBTI group (1-week online core treatment) or control group (treatment as usual).
- Participants' insomnia symptoms, anxiety, depression, and quality of life will be assessed.
- Treatment effects will be assessed at 1 week and 3 months after intervention.
- Double-blinded study design is unable to be fulfilled in the current study.

Abbreviations

CBT, Cognitive Behavioral Therapy

CI, Confidence Intervals

DBAS, Dysfunctional Beliefs and Attitudes about Sleep

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

eCBTI, e-aid Cognitive Behavior Therapy for Insomnia

ESS, Epworth Sleepiness Scale

FIRST, Ford Insomnia Response to Stress Test

HADS, Hospital Anxiety and Depression Scale

ISI, Insomnia Severity Index

ITT, Intention to Treat

LOCF, Last Observation Carried Forward

MEQ, Morningness-Eveningness Questionnaire

PP, Per Protocol

PSAS, Pre-sleep Arousal Scale

RCT, Randomized Controlled Trial

SF-12, Short-Form 12-Item Health Survey

SHPS, Sleep Hygiene and Practices Scale

TAS, Treatment Adherence Scale

TAU, Treatment as Usual

TSS, Treatment Satisfaction Scale

WMP, WeChat Mini Program

Background

Insomnia disorder

Insomnia is one of the most common sleep disorders. Most studies reported that 10-15% of adults meet the clinical diagnostic criteria for insomnia disorder [1]. On average, the economic burden of insomnia is 5010 US dollars per person per year, comparing with 421 dollars per year in an individual with good sleep, according to a study conducted in Quebec, Canada [2]. In addition, indirect consequential impairment caused by insomnia (such as work-related injuries and sickness leave) is significantly greater than direct damage (such as cost of treatment of insomnia). Moreover, insomnia is a prodromal symptom and risk factor for the development and persistence of various physical and mental disorders [3-5].

Based upon the course of illness, Insomnia is classified as 'persistent insomnia' (last three months or longer) or 'episodic insomnia' (last at least one months but less than 3 months) [6]. The diagnostic criteria for these two types of insomnia are similar, but persistent insomnia includes a minimum frequency of 'more than three nights per week' while episodic insomnia has no such criteria [6]. It is worth mentioning that episodic insomnia is a common social phenomenon, and most people would have experienced it, especially in response to situational stress or rapid changes in circadian rhythm [7]. episodic insomnia is often considered as a normal bio-psychological response with no significant impairment, episodic insomnia attracts less research attention than persistent insomnia [8]. Few longitudinal studies have investigated the natural course of insomnia. In the only two prospective studies conducted by Elis et al. specifically focusing on episodic insomnia, the annual prevalence of episodic insomnia was reported to be 36% and about 40% of the episodic insomnia patients eventually developed persistent insomnia [9, 10]. These two studies showed a high prevalence of episodic insomnia and a high susceptibility of developing long-term insomnia in those with episodic insomnia, which indicated that episodic insomnia could be a key transitional stage in the course of persistent insomnia. The findings suggested a need for developing timely, active intervention to prevent the conversion of episodic insomnia into persistent insomnia.

Whilst sleep disturbances may gradually improve in some patients once the initial stressors are resolved, a portion of patients with episodic insomnia may eventually transit to developing persistent insomnia despite the resolution of the environmental stressors [6, 11]. Due to the high recurrence rate of episodic insomnia, patients with episodic insomnia need to be actively treated. Furthermore, early psycho-behavioral interventions and/or medication are important to prevent episodic insomnia from the transition to persistent insomnia.

Cognitive behavioral therapy for insomnia (CBTI)

Currently, treatment for insomnia includes psycho-behavioral intervention and/or medication. The psycho-behavioral therapy mostly refers to Cognitive Behavioral Therapy for Insomnia (CBTI), which is a treatment approach for insomnia with a strong evidence base [12]. CBTI aims to address the cognitive and behavioral factors that perpetuate insomnia, and consists of a constellation of treatment components, such as sleep hygiene education, relaxation therapy, stimulus control, sleep restriction, and cognitive therapy [13, 14]. In addition, CBTI may increase patients' self-efficacy and confidence to control their sleep problems and is currently suggested as the first-line treatment of insomnia in adults [15]. However, traditional CBTI program mainly focuses on the maintenance factors of insomnia, thus, it is mostly applied to treat persistent insomnia [15]. A study with small sample size (n=40) by Ellis et al. showed that brief version of CBTI is effective as the treatment of acute insomnia [16]. However, little is known about whether CBTI can prevent the transition of episodic insomnia to persistent insomnia. In addition, the dissemination of CBTI may be limited due to several obstacles. For example, the treatment procedure is complex, time-consuming, and costly [17]. It typically requires patients to travel to the hospital/clinic for face-to-face treatment, which may interfere with patients' routine work. In addition, CBTI is a specialized treatment approach which should be conducted by trained therapists, there may be significant variations between different therapists and clinical settings. Without proper guidance at home, patients may not be able to effectively apply the treatment strategies (e.g. relaxation, stimulus control, sleep restriction), which in turn might hinder the resolution of insomnia. Additionally, CBTI requires patients to record their sleep pattern every night. This task might increase patient's anxiety and aggravate their insomnia symptoms. To address these challenges, internet-based CBTI has been developed and

has been receiving widespread attention in the recent years, as it makes the delivery of CBTI more efficient and flexible, and helps to overcome the above shortcomings often associated with face-to-face treatment modality [18-20]. Several e-aid CBTI (eCBTI) treatment tools have been made available in the western countries (e.g. Sleepio, SHUTi), and have shown similar efficacy as compared to standard CBTI [19, 21-24]. However, further exploration and verification are still needed to examine the efficacy of eCBTI as a treatment for episodic insomnia in Chinese population.

The current study

In this study, we plan to establish a short-term eCBTI treatment program in Chinese to test whether eCBTI can reduce the transition from episodic insomnia to persistent insomnia. Moreover, we aim to investigate whether this program can improve sleep, anxiety, depression, and quality of life in individuals with episodic insomnia.

The primary hypothesis for the trial is:

The eCBTI intervention can reduce transition of episodic insomnia to persistent insomnia;

The secondary hypotheses are:

1. The eCBTI intervention can improve sleep in patients with episodic insomnia.
2. The eCBTI intervention can improve depressive and anxiety symptoms in patients with episodic insomnia;
3. The eCBTI intervention can improve patients' overall health status and quality of life.

Methods/Design

Research design

This study is a parallel assignment, randomized controlled trial to compare eCBTI intervention versus treatment as usual (TAU). The screening, assessments, allocation, and intervention will all be carried out via a WeChat Mini Program (WMP) specially tailored for the trial. An information sheet will be provided online, and informed consent will be completed online before participation in the study. The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). The research design is summarized in Fig. 1.

Participants

We plan to recruit 200 participants diagnosed with episodic insomnia according to the sample size estimation. Participants will be recruited from sleep clinics in 31 hospital sites in mainland China, and will be randomly allocated to two groups at 1:1 ratio, namely, eCBTI (n=100, 50%) or control group (TAU) (n=100, 50%). The eCBTI group will receive eCBTI core treatment daily for 1 week in addition to TAU, while the control group will only receive TAU.

Eligibility criteria

To be included, participants must fulfill the following inclusion criteria:

A. Meeting the diagnostic criteria for episodic insomnia according to DSM-5,

B. 18 years of age or older,

C. being able to comply to the intervention,

D. Provision of electronic informed consent,

E. Own and know how to use smart gadgets (such as smartphones, tablets, and computers).

Participants will be excluded if they meet the following exclusion criteria:

A. Having a diagnosis of a significant untreated mental or medical illness (e.g. consciousness disturbances, mania, acute phase of schizophrenia, major depressive disorder, etc.),

B. Have been receiving any kind of psychological treatment for insomnia in the past 6 months,

C. Shift workers, frequent night shift workers, frequent cross-time fliers (e.g. international flight crew, shifted nurse/health professionals),

To allow for greater generalizability, this study does not exclude patients with a stable condition of somatic disease, mental disorders (e.g. depression in remission), and sleep disorders, or individuals receiving pharmacological treatments (e.g. antihypertensive drugs, antidepressants, and benzodiazepines).

Randomization

This study is a randomized controlled trial. Participants fulfilling the study criteria will be randomly allocated to either eCBTI or Control group using simple randomization (computer-generated random numbers) [25]. An independent researcher will implement randomization and treatment allocation, which will be conducted through an online system.

Blinding

Onsite-research staff will be blinded to the group assignment. The researcher who carries out the randomization procedure will be blinded to the study protocol.

Assessment points

Assessments will be conducted at week 0 (baseline), week 2 (one week post treatment), and week 12 (3-month after intervention). In consideration of ethical matters, participants in the control group will be offered eCBTI at week 12.

Planned intervention

After baseline assessment, participants will be randomly assigned to receive one-week eCBTI or to receive treatment as usual. E-CBTI will be delivered using the WeChat Mini Program. The program and all tools can be accessed using the WeChat app of any smartphone. With the assistance from several professional IT staff and clinical psychologists, the E-CBTI intervention program has been well-developed and tested before the start of our current study. Participants in the eCBTI group will receive the core sessions daily for one week. Participants will be provided with individualized treatment with the behavioral components (e.g. stimulus control, sleep restriction) according to their sleep pattern in the past 2 weeks prior to the treatment session), as well as the cognitive components (e.g. cognitive restructuring, paradoxical intention). Treatment elements also include daily sleep diary, relaxation audios (e.g. body scan,

breathing exercise), and sleep hygiene education. The treatment content is designed based on the guidelines for CBTI [13, 26, 27].

Assessment of safety

CBTI is a cognitive behavioral therapy and its risk of severe adverse events is low. Previous studies indicated that online CBTI is rather safe and did not report any adverse outcomes [28]. In the current study, participant's insomnia severity will be monitored by subjective measurements during treatment and at a 3-month follow up. Additionally, psychiatrists will be involved to assess participant's suicidal ideation, professional intervention will be provided to those in need. Participants will be allowed to attend their usual clinical follow-up in the clinic and concurrently receive routine treatments for their clinical conditions, where needed. Any participant who reports worse insomnia symptoms after the completion of intervention will be introduced to receive standard treatment for insomnia (medication and/or non-pharmaceutical treatment).

Outcome measures

Participants will receive a WeChat notification to complete the assessments online. At all times, all the assessment will be consistent across participants. If participants do not complete the questionnaire within two days, they will receive a reminder message. At baseline, demographics and related clinical data will be collected. Descriptive data on lifestyle practices such as tea and coffee consumption, smoking, and alcohol use will also be recorded.

Primary outcome measures

The Change in insomnia symptoms will be measured by the insomnia severity index (ISI) [29, 30], which assesses the severity, nature, and impact of insomnia. It is a 7-item self-report measure, ranging from 0 (no problem) to 4 (very severe problem). The resulting sum score of the ISI ranges from 0 to 28. This outcome will be measured again at week 2 (one week after treatment is complete) and week 12 (three month follow-up) in both eCBTI and Control groups.

Another primary outcome measure is the Ford Insomnia Response to Stress Test (FIRST) [31], a measure to identify sleep disturbance and predisposition to persistent insomnia. Scores on this nine-item self-report questionnaire range from 9 to 36.

Secondary outcome measures

Subjects' general sleep hygiene and practices will be measured with Sleep Hygiene and Practices Scale (SHPS) [32]. Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS) [33] will be used to measure sleep-related beliefs, potential treatments, expectations, and attitudes towards causes. Problems of sleep initiation will be assessed with the Pre-Sleep Arousal Scale (PSAS) [34]. We will also assess patient's chronotype using the 5-item Morningness-Eveningness Questionnaire (MEQ-5) [35], generic health outcomes from the patient's perspective using the 12-Item Short Form Health Survey(SF-12) [36, 37], and anxiety and depression level using the Hospital Anxiety and Depression Scale (HADS) [38]. Participants in the treatment group will be also asked to complete a self-reported questionnaire to assess their treatment adherence and perceived helpfulness using Treatment Adherence Scale (TAS) [39]. Participants' satisfaction with the treatment will be measured using Treatment Satisfaction Scale (TSS) [40].

Sample size estimation

Previous studies have indicated that approximately 40% of episodic insomnia patients transits to persistent insomnia [9, 10]. Based on our previous clinical experience, we anticipate that more than 70% of the subjects will have been retained at 12-week follow-up. In order to meet the 95% confidence intervals (CI) with 35%-49% requirement, the current project needs 200 cases of episodic insomnia. This sample size ensures the statistical effect is greater than 0.8 in continuous data of small sample (Cohen d = 0.30), and also ensures that the odds ratio (OR) of dichotomous variables is greater than 1.50 ($p>0.05$).

Statistical analysis

Intention to treat (ITT) [41] will be used for the main efficacy analysis and per protocol (PP) for the consistency test. ITT group consists of all participants who have undergone at least one week of treatment and evaluation. PP group refers to all ITT subjects who have not experienced significant program deviation or violation. In ITT analysis, last observation carried forward (LOCF) method will be used to analyze any missing therapeutic data.

Mean with standard deviation for continuous variables, and the frequency with a percentage for categorical variables will be reported. Independent t-test and non-parametric analyses,

where appropriate, will be applied to compare the differences between two groups. Repeated measurement analysis will be utilized to compare the changes of symptoms (e.g. ISI score) following treatment and at 3-month follow-up. The clinical outcome of categorical variables will be computed using survival analysis or Chi Square test, such as the appearance of suicidal ideation (as measured by 'Yes/No' question). Statistical analyses will be conducted using SPSS Analytics software v.22.0. Alpha will be set as 0.05 for all tests (2 sided).

Ethics and Dissemination

Electronic informed consent form will be signed by all participants. Participants are ensured that the participation is completely voluntary, and their information will be kept confidential. The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). Zhang bin and his research team will have access to the final dataset and make the final decision to terminate the trial. The results of the investigation will be published in scientific papers. The data from the investigation will be made available online if necessary.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research.

Discussion

episodic insomnia is a common phenomenon and might be a significant contributory causal factor in the transition from episodic insomnia to persistent insomnia. E-aid CBTI is more efficient, flexible, and time-saving compared to traditional face-to-face CBTI, and may also help to improve an individual's mood disturbance (e.g. anxiety and depressive symptoms) as well as quality of life. The main aim of the current trial is to investigate whether a brief eCBTI programme is effective to prevent the transition from acute insomnia to persistent insomnia. A previous placebo-controlled RCT demonstrated that online CBTI yields an effect size comparable to that of a traditionally delivered face to face therapy [28]. Furthermore, a previous RCT has provided some preliminary support for the efficacy of treating acute insomnia with a test of single-shot CBTI [16]. The study design benefits from being administered online with a smartphone app which is used widely in China, allowing us to recruit adequate research participants and limit researcher bias during the conduct of the study. Nonetheless, the study will test the key hypothesis that episodic insomnia is a contributory causal factor or natural course in the occurrence of persistent insomnia.

Limitation

First, double-blinded study design is unable to be fulfilled in the current study, only the onsite-research staff are blinded to the group assignment. Second, the sample size of this study is relatively small, the results might thus not be representative of the general population. Third, sleep measurements in our study are mainly based on self-reports, apart from subjective sleep measurements, objective measurements, such as actigraphy and polysomnography would be beneficial.

Trial status

Recruitment began in October 2017. It is anticipated that recruitment will be complete by October 2019, and that trial results will be available in 2020.

Funding statement

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Authors' contributions

Study Design: Bin Zhang

Drafting of the manuscript: Yuan Yang, Xian Luo, and Dhirendra Paudel

Critical revision of the manuscript: Jihui Zhang, Shirley Xin, and Bin Zhang

Approval of the final version for publication: all co-authors.

Competing interests

The authors declare that they have no competing interests.

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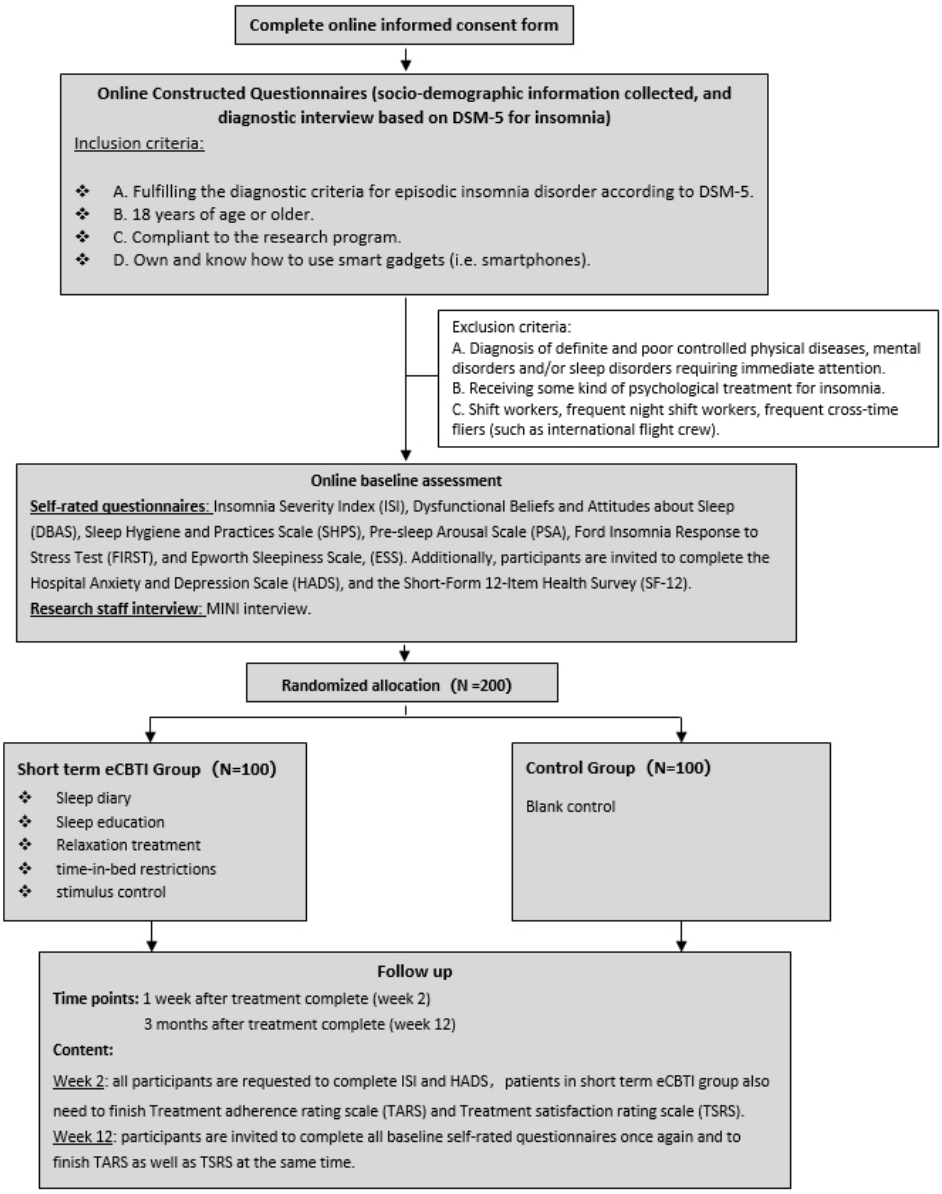
Figure legend

Figure 1 Recruitment Flowchart



Recruitment Flowchart

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description
Administrative information		
Title	1 P1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a P2	Trial identifier and registry name. If not yet registered, name of intended registry
	2b NA	All items from the World Health Organization Trial Registration Data Set
Protocol version	3 P1	Date and version identifier
Funding	4 P14	Sources and types of financial, material, and other support
Roles and responsibilities	5a P14	Names, affiliations, and roles of protocol contributors
	5b NA	Name and contact information for the trial sponsor
	5c P14	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
	5d NA	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)
Introduction		
Background and rationale	6a 5-7	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
	6b NA	Explanation for choice of comparators
Objectives	7 P7	Specific objectives or hypotheses
Trial design	8 P8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		

Study setting	9 P8	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
Eligibility criteria	10 P8	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a P9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b NA	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)
	11c NA	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d 10	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12 P10	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
Participant timeline	13 P17	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14 P11	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15 P8	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a P9	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
Allocation concealment mechanism	16b P8	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

Implementation	16c P8	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a P8	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b NA	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a P9	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
	18b NA	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
Data management	19 NA	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
Statistical methods	20a P11	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
	20b P11	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c NA	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a NA	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
	21b P12	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
Harms	22 P10	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing	23 NA	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24 P12	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25 NA	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)
Consent or assent	26a P12	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b NA	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27 P12	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
Declaration of interests	28 P14	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29 P12	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30 P10	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a P12	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
	31b NA	Authorship eligibility guidelines and any intended use of professional writers
	31c NA	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32 NA	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33 NA	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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Effects of E-aid cognitive behavioral therapy for insomnia (eCBTI) to prevent the transition from episodic insomnia to persistent insomnia: study protocol for a randomized controlled trial

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Effects of E-aid cognitive behavioral therapy for insomnia (eCBTI) to prevent the transition from episodic insomnia to persistent insomnia: study protocol for a randomized controlled trial

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Abstract

Introduction: Previous evidence suggested that online self-guided sleep intervention is efficacious in improving treatment outcomes in patients with persistent insomnia. However, the research on online sleep interventions targeting episodic insomnia has been scarce. This study aims to evaluate the effectiveness of brief e-aid cognitive behavioral therapy for insomnia (eCBTI) in preventing transition from episodic insomnia to persistent insomnia.

Methods and analysis: This is a pragmatic two-arm multi-center, randomized controlled trial comparing eCBTI with treatment as usual (TAU) in outpatients. Two hundred patients with episodic insomnia (as defined by DSM-5) will be recruited. Patients will be randomly assigned to receive one-week eCBTI via a Smartphone application, or to receive treatment as usual. Treatment effects will be assessed at 1 week and 3 months after intervention. The primary outcome of the study, whether the eCBTI program is sufficient in preventing transition from short-term to persistent insomnia, is measured by Insomnia Severity Index (ISI). Secondary outcome measurements include Dysfunctional Beliefs and Attitudes about Sleep (DBAS), Ford Insomnia Response to Stress Test (FIRST), Sleep Hygiene and Practices Scale (SHPS), Pre-sleep Arousal Scale (PSAS), and Epworth Sleepiness Scale (ESS). Additionally, Hospital Anxiety and Depression Scale (HADS) and the Short-Form 12-Item Health Survey (SF-12) will be used for the measurement of mood symptoms and quality of life.

Ethics and dissemination: The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). The results of the investigation will be published in scientific papers.

Trial registration: NCT03302455 (clinicaltrials.gov). Date of registration: October 5, 2017.

***Keywords*:** E-aid cognitive behavior therapy for insomnia (eCBTI), episodic insomnia, randomized controlled trial (RCT).

Strengths and limitations

- Participants will be randomly allocated using simple randomization (computer-generated random numbers).
- An independent researcher will implement randomization and treatment allocation through an automated online system.
- Onsite-research staff will be blinded to the group assignment and study outcomes during the entire trail.
- Statistical analyses will be carried out by an independent researcher.
- Double-blinded study design is unable to be fulfilled in the current study.

Abbreviations

CBT, Cognitive Behavioral Therapy

CI, Confidence Intervals

DBAS, Dysfunctional Beliefs and Attitudes about Sleep

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

eCBTI, e-aid Cognitive Behavior Therapy for Insomnia

ESS, Epworth Sleepiness Scale

FIRST, Ford Insomnia Response to Stress Test

HADS, Hospital Anxiety and Depression Scale

ISI, Insomnia Severity Index

ITT, Intention to Treat

LOCF, Last Observation Carried Forward

MEQ, Morningness-Eveningness Questionnaire

PP, Per Protocol

PSAS, Pre-sleep Arousal Scale

RCT, Randomized Controlled Trial

SF-12, Short-Form 12-Item Health Survey

SHPS, Sleep Hygiene and Practices Scale

TAS, Treatment Adherence Scale

TAU, Treatment as Usual

TSS, Treatment Satisfaction Scale

WMP, WeChat Mini Program

Background

Insomnia disorder

Insomnia is one of the most common sleep disorders. Most studies reported that 10-15% of adults meet the clinical diagnostic criteria for insomnia disorder [1]. On average, the economic burden of insomnia is 5010 US dollars per person per year, comparing with 421 dollars per year in an individual with good sleep, according to a study conducted in Quebec, Canada [2]. In addition, indirect consequential impairment caused by insomnia (such as work-related injuries and sickness leave) is significantly greater than direct damage (such as cost of treatment of insomnia). Moreover, insomnia is a prodromal symptom and risk factor for the development and persistence of various physical and mental disorders [3-5].

Based upon the course of illness, Insomnia is classified as 'persistent insomnia' (last three months or longer) or 'episodic insomnia' (last at least one months but less than 3 months) [6]. The diagnostic criteria for these two types of insomnia are similar, but persistent insomnia includes a minimum frequency of 'more than three nights per week' while episodic insomnia has no such criteria [6]. It is worth mentioning that episodic insomnia is a common social phenomenon, and most people would have experienced it, especially in response to situational stress or rapid changes in circadian rhythm [7]. episodic insomnia is often considered as a normal bio-psychological response with no significant impairment, episodic insomnia attracts less research attention than persistent insomnia [8]. Few longitudinal studies have investigated the natural course of insomnia. In the only two prospective studies conducted by Elis et al. specifically focusing on episodic insomnia, the annual prevalence of episodic insomnia was reported to be 36% and about 40% of the episodic insomnia patients eventually developed persistent insomnia [9, 10]. These two studies showed a high prevalence of episodic insomnia and a high susceptibility of developing long-term insomnia in those with episodic insomnia, which indicated that episodic insomnia could be a key transitional stage in the course of persistent insomnia. The findings suggested a need for developing timely, active intervention to prevent the conversion of episodic insomnia into persistent insomnia.

Whilst sleep disturbances may gradually improve in some patients once the initial stressors are resolved, a portion of patients with episodic insomnia may eventually transit to developing persistent insomnia despite the resolution of the environmental stressors [6, 11]. Due to the high recurrence rate of episodic insomnia, patients with episodic insomnia need to be actively treated. Furthermore, early psycho-behavioral interventions and/or medication are important to prevent episodic insomnia from the transition to persistent insomnia.

Cognitive behavioral therapy for insomnia (CBTI)

Currently, treatment for insomnia includes psycho-behavioral intervention and/or medication. The psycho-behavioral therapy mostly refers to Cognitive Behavioral Therapy for Insomnia (CBTI), which is a treatment approach for insomnia with a strong evidence base [12]. CBTI aims to address the cognitive and behavioral factors that perpetuate insomnia, and consists of a constellation of treatment components, such as sleep hygiene education, relaxation therapy, stimulus control, sleep restriction, and cognitive therapy [13, 14]. In addition, CBTI may increase patients' self-efficacy and confidence to control their sleep problems and is currently suggested as the first-line treatment of insomnia in adults [15]. However, traditional CBTI program mainly focuses on the maintenance factors of insomnia, thus, it is mostly applied to treat persistent insomnia [15]. A study with small sample size (n=40) by Ellis et al. showed that brief version of CBTI is effective as the treatment of acute insomnia [16]. However, little is known about whether CBTI can prevent the transition of episodic insomnia to persistent insomnia. In addition, the dissemination of CBTI may be limited due to several obstacles. For example, the treatment procedure is complex, time-consuming, and costly [17]. It typically requires patients to travel to the hospital/clinic for face-to-face treatment, which may interfere with patients' routine work. In addition, CBTI is a specialized treatment approach which should be conducted by trained therapists, there may be significant variations between different therapists and clinical settings. Without proper guidance at home, patients may not be able to effectively apply the treatment strategies (e.g. relaxation, stimulus control, sleep restriction), which in turn might hinder the resolution of insomnia. Additionally, CBTI requires patients to record their sleep pattern every night. This task might increase patient's anxiety and aggravate their insomnia symptoms. To address these challenges, internet-based CBTI has been developed and

has been receiving widespread attention in the recent years, as it makes the delivery of CBTI more efficient and flexible, and helps to overcome the above shortcomings often associated with face-to-face treatment modality [18-20]. Several e-aid CBTI (eCBTI) treatment tools have been made available in the western countries (e.g. Sleepio, SHUTi), and have shown similar efficacy as compared to standard CBTI [19, 21-24]. However, further exploration and verification are still needed to examine the efficacy of eCBTI as a treatment for episodic insomnia in Chinese population.

The current study

In this study, we plan to establish a short-term eCBTI treatment program in Chinese to test whether eCBTI can reduce the transition from episodic insomnia to persistent insomnia. Moreover, we aim to investigate whether this program can improve sleep, anxiety, depression, and quality of life in individuals with episodic insomnia.

The primary hypothesis for the trial is:

The eCBTI intervention can reduce transition of episodic insomnia to persistent insomnia;

The secondary hypotheses are:

1. The eCBTI intervention can improve sleep in patients with episodic insomnia.
2. The eCBTI intervention can improve depressive and anxiety symptoms in patients with episodic insomnia;
3. The eCBTI intervention can improve patients' overall health status and quality of life.

Methods/Design

Research design

This study is a parallel assignment, randomized controlled trial to compare eCBTI intervention versus treatment as usual (TAU). The screening, assessments, allocation, and intervention will all be carried out via a WeChat Mini Program (WMP) specially tailored for the trial. An information sheet will be provided online, and informed consent will be completed online before participation in the study. The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). The research design is summarized in Fig. 1.

Participants

We plan to recruit 200 participants diagnosed with episodic insomnia according to the sample size estimation. Participants will be recruited from sleep clinics in 31 hospital sites in mainland China, and will be randomly allocated to two groups at 1:1 ratio, namely, eCBTI (n=100, 50%) or control group (TAU) (n=100, 50%). The eCBTI group will receive eCBTI core treatment daily for 1 week in addition to TAU, while the control group will only receive TAU.

Eligibility criteria

To be included, participants must fulfill the following inclusion criteria:

A. Meeting the diagnostic criteria for episodic insomnia according to DSM-5,

B. 18 years of age or older,

C. being able to comply to the intervention,

D. Provision of electronic informed consent,

E. Own and know how to use smart gadgets (such as smartphones, tablets, and computers).

Participants will be excluded if they meet the following exclusion criteria:

A. Having a diagnosis of a significant untreated mental or medical illness (e.g. consciousness disturbances, mania, acute phase of schizophrenia, major depressive disorder, etc.),

B. Have been receiving any kind of psychological treatment for insomnia in the past 6 months,

C. Shift workers, frequent night shift workers, frequent cross-time fliers (e.g. international flight crew, shifted nurse/health professionals),

To allow for greater generalizability, this study does not exclude patients with a stable condition of somatic disease, mental disorders (e.g. depression in remission), and sleep disorders, or individuals receiving pharmacological treatments (e.g. antihypertensive drugs, antidepressants, and benzodiazepines).

Randomization

This study is a randomized controlled trial. Participants fulfilling the study criteria will be randomly allocated to either eCBTI or Control group using simple randomization (computer-generated random numbers) [25]. An independent researcher from IT department will implement randomization and treatment allocation, which will be conducted through an automated online system. The research team will not be able to influence randomization and have no access to allocations.

Blindness of assessment and analysis

Onsite-research staff will be blinded to the group assignment and study hypotheses of the trial. The independent researcher from IT department who carries out the randomization and allocation procedure will be blinded to the study protocol. Participants could not be blinded to treatment allocation as participants in blank control group only receive TAU. The research team will have limited contact with both IT staff and study participants therefore will not be able to bias the allocation or the assessments. Statistical analyses will be carried out by an independent researcher from the Southern Medical University who are not involved in the procedures of randomization and assessment.

Assessment points

Assessments will be conducted at week 0 (baseline), week 2 (one week post treatment), and week 12 (3-month after intervention). In consideration of ethical matters, participants in the control group will be offered eCBTI at week 12.

Planned intervention

After baseline assessment, participants will be randomly assigned to receive one-week eCBTI or to receive treatment as usual. E-CBTI will be delivered using the WeChat Mini Program. The

program and all tools can be accessed using the WeChat app of any smartphone. With the assistance from several professional IT staff and clinical psychologists, the E-CBTI intervention program has been well-developed and tested before the start of our current study. Participants in the eCBTI group will receive the core sessions daily for one week. Participants will be provided with individualized treatment with the behavioral components (e.g. stimulus control, sleep restriction) according to their sleep pattern in the past 2 weeks prior to the treatment session), as well as the cognitive components (e.g. cognitive restructuring, paradoxical intention). Treatment elements also include daily sleep diary, relaxation audios (e.g. body scan, breathing exercise), and sleep hygiene education. The treatment content is designed based on the guidelines for CBTI [13, 26, 27].

Assessment of safety

CBTI is a cognitive behavioral therapy and its risk of severe adverse events is low. Previous studies indicated that online CBTI is rather safe and did not report any adverse outcomes [28]. In the current study, participant's insomnia severity will be monitored by subjective measurements during treatment and at a 3-month follow up. Additionally, psychiatrists will be involved to assess participant's suicidal ideation, professional intervention will be provided to those in need. Participants will be allowed to attend their usual clinical follow-up in the clinic and concurrently receive routine treatments for their clinical conditions, where needed. Any participant who reports worse insomnia symptoms after the completion of intervention will be introduced to receive standard treatment for insomnia (medication and/or non-pharmaceutical treatment).

Outcome measures

Participants will receive a WeChat notification to complete the assessments online. At all times, all the assessment will be consistent across participants. If participants do not complete the questionnaire within two days, they will receive a reminder message. At baseline, demographics and related clinical data will be collected. Descriptive data on lifestyle practices such as tea and coffee consumption, smoking, and alcohol use will also be recorded.

Primary outcome measures

The Change in insomnia symptoms will be measured by the insomnia severity index (ISI) [29, 30], which assesses the severity, nature, and impact of insomnia. It is a 7-item self-report measure, ranging from 0 (no problem) to 4 (very severe problem). The resulting sum score of the ISI ranges from 0 to 28. This outcome will be measured again at week 2 (one week after treatment is complete) and week 12 (three month follow-up) in both eCBTI and Control groups. Another primary outcome measure is the Ford Insomnia Response to Stress Test (FIRST) [31], a measure to identify sleep disturbance and predisposition to persistent insomnia. Scores on this nine-item self-report questionnaire range from 9 to 36.

Secondary outcome measures

Subjects' general sleep hygiene and practices will be measured with Sleep Hygiene and Practices Scale (SHPS) [32]. Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS) [33] will be used to measure sleep-related beliefs, potential treatments, expectations, and attitudes towards causes. Problems of sleep initiation will be assessed with the Pre-Sleep Arousal Scale (PSAS) [34]. We will also assess patient's chronotype using the 5-item Morningness-Eveningness Questionnaire (MEQ-5) [35], generic health outcomes from the patient's perspective using the 12-Item Short Form Health Survey(SF-12) [36, 37], and anxiety and depression level using the Hospital Anxiety and Depression Scale (HADS) [38]. Participants in the treatment group will be also asked to complete a self-reported questionnaire to assess their treatment adherence and perceived helpfulness using Treatment Adherence Scale (TAS) [39]. Participants' satisfaction with the treatment will be measured using Treatment Satisfaction Scale (TSS) [40].

Sample size estimation

Previous studies have indicated that approximately 40% of episodic insomnia patients transits to persistent insomnia [9, 10]. Based on our previous clinical experience, we anticipate that more than 70% of the subjects will have been retained at 12-week follow-up. In order to meet the 95% confidence intervals (CI) with 35%-49% requirement, the current project needs 200 cases of episodic insomnia. This sample size ensures the statistical effect is greater than 0.8 in

continuous data of small sample (Cohen d = 0.30), and also ensures that the odds ratio (OR) of dichotomous variables is greater than 1.50 (p>0.05).

Statistical analysis

Intention to treat (ITT) [41] will be used for the main efficacy analysis and per protocol (PP) for the consistency test. ITT group consists of all participants who have undergone at least one week of treatment and evaluation. PP group refers to all ITT subjects who have not experienced significant program deviation or violation. In ITT analysis, last observation carried forward (LOCF) method will be used to analyze any missing therapeutic data.

Mean with standard deviation for continuous variables, and the frequency with a percentage for categorical variables will be reported. Independent t-test and non-parametric analyses, where appropriate, will be applied to compare the differences between two groups. Repeated measurement analysis will be utilized to compare the changes of symptoms (e.g. ISI score) following treatment and at 3-month follow-up. The clinical outcome of categorical variables will be computed using survival analysis or Chi Square test, such as the appearance of suicidal ideation (as measured by 'Yes/No' question). Statistical analyses will be conducted using SPSS Analytics software v.22.0. Alpha will be set as 0.05 for all tests (2 sided).

Ethics and Dissemination

Electronic informed consent form will be signed by all participants. Participants are ensured that the participation is completely voluntary, and their information will be kept confidential. The ethical approval for the study has been obtained from Ethics Committee of Southern Medical University (reference number: NFEC-2017-131). Zhang bin and his research team will have access to the final dataset and make the final decision to terminate the trial. The results of the investigation will be published in scientific papers. The data from the investigation will be made available online if necessary.

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research.

Discussion

episodic insomnia is a common phenomenon and might be a significant contributory causal factor in the transition from episodic insomnia to persistent insomnia. E-aid CBTI is more efficient, flexible, and time-saving compared to traditional face-to-face CBTI, and may also help to improve an individual's mood disturbance (e.g. anxiety and depressive symptoms) as well as quality of life. The main aim of the current trial is to investigate whether a brief eCBTI programme is effective to prevent the transition from acute insomnia to persistent insomnia. A previous placebo-controlled RCT demonstrated that online CBTI yields an effect size comparable to that of a traditionally delivered face to face therapy [28]. Furthermore, a previous RCT has provided some preliminary support for the efficacy of treating acute insomnia with a test of single-shot CBTI [16]. The study design benefits from being administered online with a smartphone app which is used widely in China, allowing us to recruit adequate research participants and limit researcher bias during the conduct of the study. Nonetheless, the study will test the key hypothesis that episodic insomnia is a contributory causal factor or natural course in the occurrence of persistent insomnia.

Limitation

First, double-blinded study design is unable to be fulfilled in the current study, only the onsite-research staff are blinded to the group assignment. Second, the sample size of this study is relatively small, the results might thus not be representative of the general population. Third, sleep measurements in our study are mainly based on self-reports, apart from subjective sleep measurements, objective measurements, such as actigraphy and polysomnography would be beneficial.

Trial status

Recruitment began in October 2017. It is anticipated that recruitment will be complete by October 2019, and that trial results will be available in 2020.

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Authors' contributions

Study Design: Bin Zhang

Drafting of the manuscript: Yuan Yang, Xian Luo, and Dhirendra Paudel

Critical revision of the manuscript: Jihui Zhang, Shirley Xin, and Bin Zhang

Approval of the final version for publication: all co-authors.

Competing interests

The authors declare that they have no competing interests.

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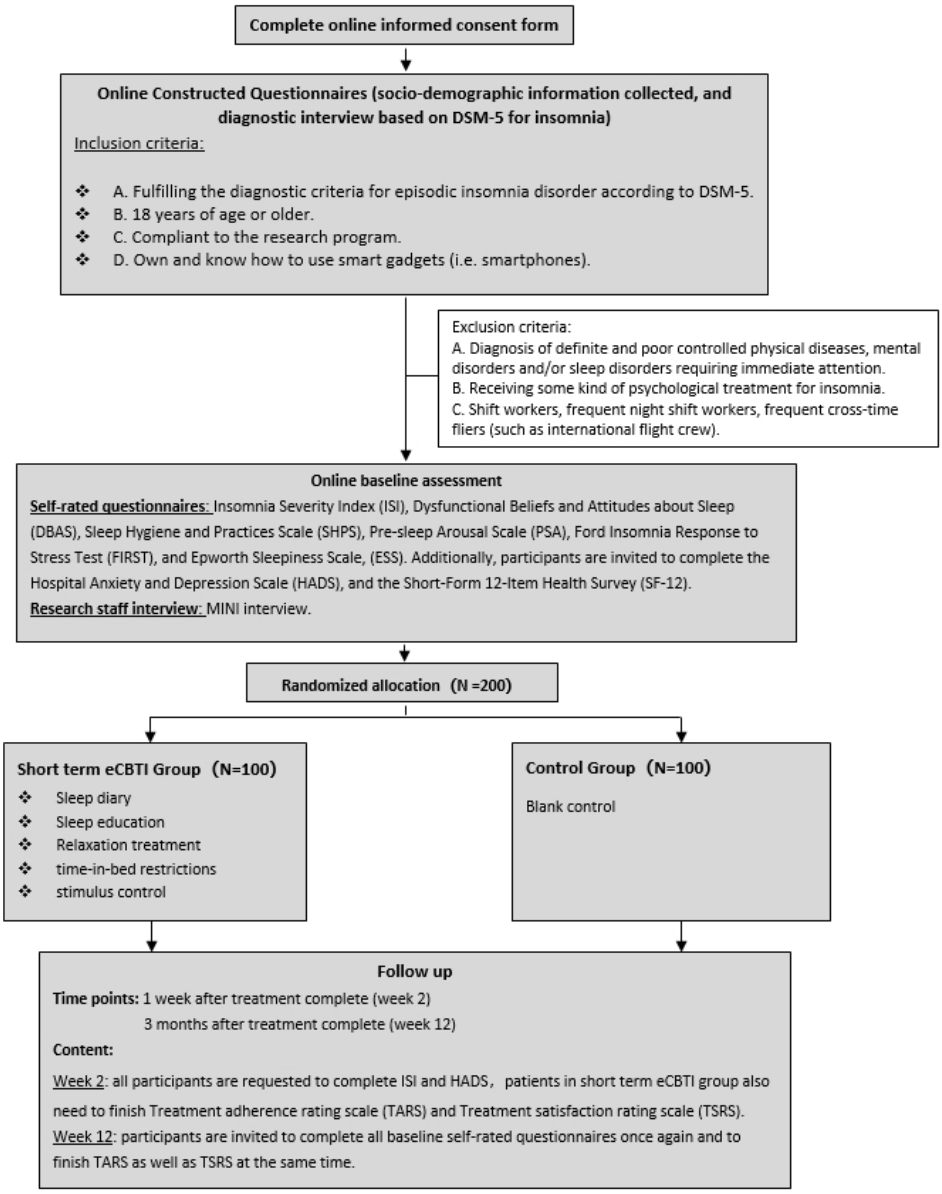
Figure legend

Figure 1 Recruitment Flowchart



Recruitment Flowchart

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description
Administrative information		
Title	1 P1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a P2	Trial identifier and registry name. If not yet registered, name of intended registry
	2b NA	All items from the World Health Organization Trial Registration Data Set
Protocol version	3 P1	Date and version identifier
Funding	4 P14	Sources and types of financial, material, and other support
Roles and responsibilities	5a P14	Names, affiliations, and roles of protocol contributors
	5b NA	Name and contact information for the trial sponsor
	5c P14	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
	5d NA	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)
Introduction		
Background and rationale	6a 5-7	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
	6b NA	Explanation for choice of comparators
Objectives	7 P7	Specific objectives or hypotheses
Trial design	8 P8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		

Study setting	9 P8	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
Eligibility criteria	10 P8	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a P9	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b NA	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)
	11c NA	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d 10	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12 P10	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
Participant timeline	13 P17	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14 P11	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15 P8	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a P9	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
Allocation concealment mechanism	16b P8	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

Implementation	16c P8	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a P8	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b NA	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a P9	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
	18b NA	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
Data management	19 NA	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
Statistical methods	20a P11	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
	20b P11	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c NA	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a NA	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
	21b P12	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
Harms	22 P10	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing	23 NA	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24 P12	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25 NA	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)
Consent or assent	26a P12	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b NA	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27 P12	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
Declaration of interests	28 P14	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29 P12	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30 P10	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a P12	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
	31b NA	Authorship eligibility guidelines and any intended use of professional writers
	31c NA	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32 NA	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33 NA	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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.