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## Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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|-------------------------------|--|
| Journal:                      | <i>BMJ Open</i>  |
| Manuscript ID                 | bmjopen-2022-063442  |
| Article Type:                 | Protocol   |
| Date Submitted by the Author: | 12-Apr-2022  |
| Complete List of Authors:     | Pei, Wenya; Sun Yat-sen University First Affiliated Hospital<br>He, Te; South China University of Technology<br>Yang, Pei; South China University of Technology<br>Lv, Xiaozhou; Sun Yat-sen University First Affiliated Hospital<br>Jiao, Boyu; Sun Yat-sen University First Affiliated Hospital<br>Meng, Fanqi; Sun Yat-sen University First Affiliated Hospital<br>Yan, Yingshuo; Sun Yat-sen University First Affiliated Hospital<br>Cui, Liqian; Sun Yat-sen University First Affiliated Hospital<br>He, Guanheng; Sun Yat-sen University First Affiliated Hospital<br>Zhou, Xin; Sun Yat-sen University First Affiliated Hospital<br>Wen, Guihua; South China University of Technology<br>Ruan, Jingwen; Sun Yat-sen University First Affiliated Hospital,<br>Lu, Liming; Guangzhou University of Chinese Medicine |
| Keywords:                     | CLINICAL PHYSIOLOGY, Rehabilitation medicine < INTERNAL MEDICINE, COMPLEMENTARY MEDICINE   |
|                               |  |

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Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in  
patients with insomnia: study protocol for a randomized controlled trial

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## Abstract

### Introduction

Insomnia affects physical and mental health due to the lack of continuous and complete sleep architecture. Polysomnograms (PSGs) are used to record electrical information to perform sleep architecture using deep learning. Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) could not only improve sleep quality, solve anxiety, depression but also ameliorate poor sleep habits and detrimental cognition. However, the clinical mechanism of this process remain unclear.

### Methods and analysis

This randomized controlled trial will evaluate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia. Participants will be randomized to receive either electroacupuncture combined with CBT-I or sham acupuncture combined with CBT-I and followed up for four weeks. The primary outcome is sleep quality, which is evaluated by the Pittsburgh sleep quality index(PSQI). The secondary outcome measures include a measurement of depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events. Sleep architecture will be assessed using deep learning on PSGs.

### Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals.

### Trial registration number

CTR2100052502

**Keywords:** insomnia, cognitive behavioral therapy for insomnia, electroacupuncture, randomized controlled trial

#### Strengths and limitations of this study

- This study will investigate the efficacy and effectiveness of electroacupuncture combined with CBT-I.
- We will observe the effects of electroacupuncture combined with CBT-I on sleep quality and sleep beliefs and attitudes of patients with insomnia.
- We will use deep learning to observe the effects of electroacupuncture combined with CBT-I on sleep architecture in different dimensions.

## Introduction

Insomnia is characterized by difficulties in initiating or maintaining sleep or impaired daytime functioning, which impact both physical and mental health<sup>[1-3]</sup>. The lack of continuous and complete sleep architecture due to long-term fragmented and light sleep in patients with insomnia causes a decrease in sleep quality, which affects daily functions, and even induces anxiety, depression, and other mental symptoms<sup>[4-6]</sup>. With the increasing pressures in daily life and work, insomnia is becoming a public health problem that needs to be solved urgently as it worsens the quality of life of patients, burdens caregivers, and increases social and economic costs<sup>[7-9]</sup>.

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for insomnia and may improve sleep quality and alleviate poor sleep cognition in patients with insomnia<sup>[10-12]</sup>. During the early stage of treatment, the sleep quality of patients with severe anxiety were improved slowly and the compliance of these patients were poor. Thus, as confirmed in previous studies, acupuncture combined with CBT-I could not only solve anxiety, depression, and other emotions caused by insomnia but also ameliorate poor sleep habits and detrimental cognition<sup>[13-16]</sup>.

However, there is a lack of rigorous clinical evidence on the treatment of insomnia with acupuncture combined with CBT-I; moreover, the clinical mechanism is unclear. In previous studies, we found that by analyzing polysomnograms (PSGs), electroacupuncture improves sleep architecture and prolongs the duration of slow-wave and rapid-eye-movement (REM) sleep<sup>[17,18]</sup>. But whether acupuncture combined with CBT-I improves sleep architecture requires further research.

During the past decade, the application of deep learning to automatic sleep staging using PSGs has shown promise for understanding the macrostructure of sleep. Deep learning allows the automatic extraction of features from data related to classification tasks, and the performance of deep neural networks continues to improve as the size of the dataset increases<sup>[19-21]</sup>.

Using a high-performance automatic sleep staging algorithm to analyze PSGs recordings via deep learning, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. Furthermore, this research will provide guidance for electroacupuncture combined with CBT-I using artificial intelligence.

## Methods

### Study design

The study will be an assessor-blinded, randomized controlled trial. The protocol was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). We will follow the Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines for the design and reporting of the trial<sup>[22, 23]</sup>. The flowchart of the trial is presented in Figure 1, and the schedule of enrolment, interventions, and outcome assessments are presented in Table 1.

Sample size calculations: Referring to the previous literature<sup>[24]</sup>, we assume that the expected PSQI value of the observation group is  $9.45 \pm 1.84$  and the control  $6.43 \pm 2.10$ . We determine that a sample size of 11 per group would provide a power of 90% and an alpha level of 0.05, which would allow us to detect a difference in PSQI score between the two groups. Allowing for a 20% dropout rate, a sample size of 30 in each group is sufficient to meet statistical requirements.

### Randomization, allocation, and blinding

Patients who are interested in participating in the trial will initially be screened by phone and then asked to participate in a face-to-face interview to conduct further surveys. After recruiting all participants, random numbers will be generated and assigned by a central randomization system of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. The researcher who will screen the eligible patients after baseline

Table 1 Research flow chart

| Project                              | Screening                     | Observation phase            |                            |                            | Follow-up phase            |                     |
|--------------------------------------|-------------------------------|------------------------------|----------------------------|----------------------------|----------------------------|---------------------|
|                                      | assessment 0<br>pre-treatment | Assession 1<br>pre-treatment | Assession 2<br>Week 2±1day | Assession 3<br>Week 4±2day | Assession 4<br>Week 8±2day | Unplanned follow-up |
| Medical history collection           | √                             | -                            | -                          | -                          | -                          |                     |
| Sign the informed consent form       | √                             | -                            | -                          | -                          | -                          |                     |
| Inclusion criteria                   | √                             | -                            | -                          | -                          | -                          |                     |
| Exclusion criteria                   | √                             | -                            | -                          | -                          | -                          |                     |
| Basic Information                    | √                             | -                            | -                          | -                          | -                          |                     |
| Vital signs                          | √                             | √                            | √                          | √                          | √                          | ※                   |
| Index of laboratory inspection       | ※                             | ※                            | ※                          | ※                          | ※                          |                     |
| PSG                                  | -                             | √                            | -                          | √                          | -                          |                     |
| Pittsburgh sleep quality index(PSQI) | -                             | √                            | √                          | √                          | √                          |                     |
| Beck depression inventory(BDI)       | -                             | √                            | √                          | √                          | √                          |                     |
| Beck anxiety inventory(BAI)          | -                             | √                            | √                          | √                          | √                          |                     |
| DBAS-16                              | -                             | √                            | √                          | √                          | √                          |                     |
| Adverse Events                       | -                             | ※                            | ※                          | ※                          | ※                          | ※                   |
| Medication records                   | -                             | √                            | √                          | √                          | √                          |                     |
| Terminate test evaluation            | -                             | ※                            | ※                          | ※                          | ※                          |                     |

Notes: “※”Record when necessary; PSG: Long-term scalp electroencephalogram recording; DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep Scale 16 versio



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4 will assign patients to either the treatment or control group. Researchers, which include  
5  
6 statisticians, outcome assessors, and data analysts, will all be blinded to patients' group  
7  
8 assignments. Although acupuncturists will be not blinded to group assignment, they will  
9  
10 not be involved in outcome assessments or data analyses. In addition, all researchers will  
11  
12 undergo training for specific procedures before the trial begins.

### 13 **Participants and recruitment**

14  
15 Patients will be recruited using hospital-based advertisements in the Department of  
16  
17 Acupuncture and Department of Neurology of the First Affiliated Hospital of Sun  
18  
19 Yat-sen University from January 2022 to December 2025.

20  
21 The inclusion criteria will be as follows: (1) meets diagnostic criteria for insomnia  
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23 based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition<sup>[25]</sup>  
24  
25 and the International Classification of Sleep Disorders, Third Edition<sup>[26]</sup>, (2) aged 18–65  
26  
27 years, (3) experienced insomnia for more than 1 month but less than 2 years before the  
28  
29 start of the trial, (4) voluntarily agrees to participate in the investigation and provides  
30  
31 written informed consent before the clinical trial starts.

32  
33 The exclusion criteria will be as follows: (1) serious cardiovascular, liver, kidney, or  
34  
35 hematopoietic system disease, (2) insomnia was caused by a nervous system disease (e.g.,  
36  
37 stroke or Parkinson's disease), (3) insomnia was caused by a mental disorder, such as  
38  
39 depression or anxiety, (4) history of sleep apnea, (5) pregnant or lactating women, (6)  
40  
41 have received or currently receiving CBT-I.

42  
43 Withdrawal criteria will be as follows: (1) patient withdrawal from the trial because  
44  
45 of personal reasons, (2) patient has an adverse reaction related to acupuncture and refuses  
46  
47 to continue treatment, (3) during the follow-up period, the patient cannot be contacted  
48  
49 because of change of address and telephone number.

### 50 **Intervention**

51  
52 The intervention will begin the day following randomization. All participants will receive  
53  
54 20 treatments (five times per week for 4 weeks).  
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## Observation group

### Acupuncture treatment

Patients' skin will be disinfected with 75% alcohol, and patients will be asked to lie supine and wear eye masks for a better curative effect. Each participant will receive acupuncture treatment from the same acupuncturist who has more than 5 years of clinical experience in acupuncture therapy. The temperature of the treatment room will not be lower than 25°C. Each treatment will last for 30 min.

Patients in the acupuncture group will receive electroacupuncture treatment on Sishenchong (EX-HN1), bilateral Neiguan (PC6), bilateral Taixi (KI3), bilateral Shenmen (HT7), and bilateral Sanyinjiao (SP6). Tube-guided acupuncture needles will be inserted to a depth of 17-25 mm at each acupoint (acupuncture location and method for each acupoint are provided in Table 2). A low-frequency electronic pulse therapy instrument (G6805-2A, Shanghai Huayi Medical Instrument Co., Shanghai, China) will be used between the two sets of acupoints.

### CBT-I treatment

CBT-I will be given while acupuncture treatment is in progress. The intervention will consist of behavioral components (e.g. sleep restriction and stimulus control), cognitive components (e.g., cognitive restructuring and paradoxical intention), progressive muscle relaxation, and sleep hygiene<sup>[27]</sup>.

## Control group

The procedure for the control group will be the same as that for the observation group, with the major difference in interventions between the two groups being the tube needling method, in which no needle will be inserted through the tube for patients in the control group. To mimic the sensation of a real needle being inserted into the body, the acupuncturist will place the tube close to the skin at the acupoint and tap the top of the tube.

## Quality control

Table 2 Acupuncture location and method for each acupoint

| Acupoint             | Location   | Needling method  |
|----------------------|--|--|
| Sishenchong (EX-HN1) | On the parietal region, 1 cun anterior, posterior and lateral to Baihui, 4 acupoints totally.  | The angle between the needle tip and the scalp is 30°. Move the needle tip backward along the anteriore posterior midline, and then insert the needle 0.5 cun. |
| Neiguan(PC6)         | On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist. | Puncture perpendicularly 1-1.5 cun.  |
| Taixi (KI3)          | In the depression between the tip of the medial malleolus and the Achilles tendon.   | Puncture perpendicularly 0.5-1 cun.  |
| Shenmen (HT7)        | On the palmar ulnar end of the transverse crease of the wrist, and on the radial aspect of the tendon of the ulnar flexor m. of the wrist.             | Puncture perpendicularly 0.5-1 cun.  |
| Sanyinjiao (SP6)     | Posterior to the mesial border of the tibia, and 3 cun above the tip of the medial malleolus   | Puncture perpendicularly 1-1.5 cun.  |

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4 The trial will be conducted under the supervision of the First Affiliated Hospital of Sun  
5 Yat-sun University. A qualified clinical trial expert will be invited to monitor the study to  
6 identify problems during the trial, examine collected data, and control bias.  
7  
8

## 9 **Outcome measures**

### 10 **Primary outcome**

11 Pittsburgh sleep quality index

12  
13 The Pittsburgh sleep quality index (PSQI) is an internationally established tool that is  
14 used to evaluate sleep quality. The scale includes seven dimensions that consist of  
15 subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep  
16 disturbances, sleeping medication, and daytime dysfunction. The score correlates  
17 adversely with sleep quality which a higher score means the sleep quality is worse, and  
18 each factor has a score of 0 to 3 to provide a total score of 21 points<sup>[28, 29]</sup>.  
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### 27 **Secondary outcomes**

#### 28 **The Beck depression inventory**

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30 The Beck depression inventory (BDI) is a valid self-assessment index to measure  
31 depression severity and consists of 13 items. Each item is scored from 0 to 3 (0 to 4  
32 indicates no depression, 5 to 7 indicates mild depression, 8 to 15 indicates moderate  
33 depression), with a score of 16 points or more considered as severe depression<sup>[30-32]</sup>.  
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#### 39 **The Beck anxiety inventory**

40  
41 The Beck anxiety inventory (BAI) is used to assess the degree of anxiety and consists of  
42 21 items scored from 1 to 4 (15 to 25 points indicates mild anxiety, 26 to 35 points  
43 indicates moderate anxiety, and 36 points is considered severe anxiety)<sup>[33, 34]</sup>.  
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#### 47 **The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version**

48  
49 The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version (DBAS-16) is used  
50 to evaluate maladaptive cognitions associated with sleep. There are 16 items in the index,  
51 which are divided into four factors comprising consequences of insomnia, worry about  
52 sleep, sleep expectations, and medication. These factors are scored on a scale of 1–5  
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(strongly disagree to strongly agree). The total score is positively correlated with the reasonableness of sleep beliefs and attitudes<sup>[35, 36]</sup>.

### **Sleep staging**

The PARADISEP&D9600 (U.S.) Polysomnography Monitoring and Analysis System will be used to simultaneously monitor EEG, EOG, and EMG. A large clinical dataset of PSG recordings will be used to train a hybrid convolutional neural network (CNN) and recurrent neural network (RNN) to learn effective and generalizable features for sleep stage scoring<sup>[37, 38]</sup>. Then clinical data will be used to indentify the deep learning algorithm. Sleep staging for both datasets will be performed by expert sleep technicians in nonoverlapping 30-s epochs according to standards by the American Academy of Sleep Medicine(AASM), as one of five stages: wake(W), non-rapid eye movement(REM) stage 1(N1), non-REM stage 2(N2), non-REM stage 3(N3), and rapid eye movement (REM)<sup>[39]</sup>.

### **Adverse events**

During treatment and four week after treatment, a questionnaire will be administered to evaluate the various discomforts that may be caused by acupuncture: hangover, addiction, tolerance, fatigue after waking, insomnia rebound, daytime alertness, cognitive function, and behavior ability.

### **Patients and public involvement**

Patients and the public are not involved in the design or conduct of the study or the outcome measures, and no attempt will be made to assess the burden of the intervention on the patients themselves. The results of this study will be disseminated to study participants via the website of our hospitals.

### **Statistical analysis**

All analyses will be performed on the intention-to-treat population of participants who had at least one treatment. Missing data will be replaced according to the principle of the last observation carried forward. Data analyses will be performed using the SPSS version

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4 25 (IBM Corp.) software. All available data will be analyzed descriptively. For  
5 continuous data, the normality test will be applied at the beginning of the analysis.  
6 Results will be presented as means, standard deviations, and 95% confidence intervals  
7 (CIs) for continuous data that conform to the normal distribution and medians, quartiles,  
8 and ranges for rank data and continuous data that are not normally distributed. Discrete  
9 data will be presented as percentages.  
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15 We will first examine the descriptive data for sample characteristics at baseline, and  
16 independent samples t-tests will be used to compare groups for continuous variables,  
17 whereas chi-square analysis will be used to compare groups for dichotomous variables.  
18 Second, we will perform two series of repeated-measures and univariate analyses of  
19 covariance (ANCOVA) models to examine treatment effects. We will use  
20 repeated-measures ANCOVAs to analyze the primary and secondary outcome measures  
21 (i.e., PSQI, BDI, BAI, DBAS-16, and sleep staging scores) from pre-treatment to  
22 post-treatment. If a significant effect is observed, we will conduct posthoc paired samples  
23 t-tests to examine within-group changes in study outcomes. For all study outcomes, we  
24 will then perform univariate ANCOVAs to test for group differences in post-treatment  
25 values while controlling for relevant covariates. This process will be repeated to examine  
26 changes in study outcomes from pretreatment to postnatal follow-up.  
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38 When necessary, sensitivity analysis will be used to assess the robustness of the  
39 conclusions of the entire clinical trial. To evaluate the consistency of the trial and explore  
40 the factors that affect efficacy or prognosis, subgroup analysis will be conducted to  
41 identify the population with better efficacy. Safety analysis will be used to assess the  
42 incidence of adverse events and related symptoms in patients with insomnia during  
43 treatment and follow-up.  
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## Discussion

Currently, the main treatments recommended for insomnia are non-pharmaceutical and pharmaceutical treatments. Pharmaceutical treatments include benzodiazepines as well as new non-benzodiazepine drugs, which can shorten the latency to fall asleep and prolong total sleep time but also affect normal sleep physiology and cause adverse reactions<sup>[40, 41]</sup>. CBT-I, which is recommended as a first-line treatment for insomnia by the European insomnia guidelines, is limited in clinical practice because of insufficient professional therapists and poor compliance of patients with insomnia, especially in developing countries such as China<sup>[42-44]</sup>.

As a complementary alternative therapy with a long history in China, acupuncture has been used as a clinical treatment for insomnia with fewer adverse effects and less permanent damage. Previous studies showed that either acupuncture or CBT-I could produce clinically meaningful improvements in insomnia symptoms, and our preliminary research have confirmed that acupuncture combined with CBT-I also alleviate not only insomnia symptoms but also negative emotions such as anxiety and depression<sup>[13, 14, 16]</sup>. But whether acupuncture combined with CBT-I could influence sleep habits and correct cognition, and what the clinic clinical mechanism worth further research.

To ameliorate sleep habits, correct cognition, and alleviate anxiety, depression, and other emotions caused by insomnia, this study will use electroacupuncture combined with CBT-I and observe sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. In this study, PSQI will be used to assess the sleep quality, BDI and BAI will be used to evaluate the depression severity and anxiety. At the same time, we will use DBAS-16 to evaluate the sleep beliefs and attitudes before and after treatment. Because of the particularity of acupuncture therapy, the implementation of blinding is difficult in clinical research<sup>[45, 46]</sup>. A research team composed of researchers, therapists, testers, and statisticians will be established to reduce any bias that may occur



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4 during the research process by blinding testers and statisticians. This study will provide  
5 clinical evidence for the effect and safety of electroacupuncture combined with CBT-I  
6 and provide a decision-making reference for clinicians, patients, and policymakers.  
7

8  
9 To analyze the effects of electroacupuncture combined with CBT-I on sleep  
10 architecture and sleep quality in patients with insomnia, deep learning will be used to  
11 analyze PSGs in various clinical settings in this study. PSGs are used widely for clinical  
12 evaluation because they are more sensitive than routine EEGs (typically 30–60 min  
13 duration) in capturing paroxysmal electrical abnormalities<sup>[47, 48]</sup>. During the past decade,  
14 there have been various advances in automated sleep staging of PSGs data using the  
15 ability of deep learning methods to automatically extract features from data that are  
16 relevant to the classification; moreover, the performance of deep neural networks  
17 continues to improve as datasets become larger<sup>[49-52]</sup>. Using deep learning, this study will  
18 develop a high-performing, reference channel-free, automated sleep staging algorithm to  
19 analyze the sleep architecture which will provide a clinical mechanism in artificial  
20 intelligence.  
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33 In summary, this study will use electroacupuncture combined with CBT-I to treat  
34 insomnia and observe the sleep beliefs and attitudes of patients with insomnia in different  
35 dimensions using deep learning. Moreover, we will provide a solid research basis for the  
36 combined application of electroacupuncture and CBT-I for insomnia in the clinic.  
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#### 42 Acknowledgments

43 Not applicable.  
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#### 48 Footnotes

49 Contributors: Wenya Pei and Te He designed the trial protocol and drafted the manuscript.  
50 Liming Lu, Jingwen Ruan, and Guihua Wen revised the manuscript. Pei Yang, Xiaozhou  
51 Lv, and Boyu Jiao will plan the data analysis. Liqian Cui, Yingshuo Yan, Fanqi Meng,  
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4 Guanheng He, and Xin Zhou will participate in participant recruitment. All authors  
5 discussed, read, and revised the manuscript, and all approved the publication of this  
6 protocol.  
7

8  
9 Funding: The study was supported by the Key R&D Program of Guangdong Province  
10 (2020B1111120001).  
11

12  
13 Competing interests: None declared.  
14

15 Patient consent for publication: Not applicable  
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17 Provenance and peer review: Not commissioned; externally peer-reviewed.  
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21 Ethics statements  
22

23 Patient consent for publication  
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25 Not applicable.  
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27 Ethics approval and consent to participate: The study was approved by the ethics  
28 committee of the First Affiliated Hospital of Sun Yat-sun University (2021763).  
29

30 Participants will be included only after they provide written informed consent. The study  
31 was registered in the Chinese Clinical Trial Registry (No.ChiCTR2100052502,  
32 30/10/2021).  
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## 36 37 38 **References** 39

- 40  
41 1. Punnoose AR, Golub RM, Burke AE. JAMA patient page. Insomnia. JAMA  
42 2012;307(24):2653.  
43
- 44 2. Merrigan JM, Buysse DJ, Bird JC, et al. JAMA patient page. Insomnia. JAMA  
45 2013;309(7):733.  
46  
47
- 48 3. Roth T. Insomnia: Definition, prevalence, etiology, and consequences. J Clin Sleep  
49 Med 2007;3(Suppl 5):S7–10.  
50  
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59  
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2  
3  
4 4. Kalmbach DA, Anderson JR, Drake CL. The impact of stress on sleep: Pathogenic  
5 sleep reactivity as a vulnerability to insomnia and circadian disorders. *J Sleep Res* 2018;  
6 27(6):e12710.  
7
- 8  
9 5. Shekleton JA, Flynn-Evans EE, Miller B, et al. Neurobehavioral performance  
10 impairment in insomnia: relationships with self-reported sleep and daytime functioning.  
11 *Sleep* 2014;37(1):107–16.  
12
- 13  
14 6. Cross NE, Carrier J, Postuma RB, et al. Association between insomnia disorder and  
15 cognitive function in middle-aged and older adults: A cross-sectional analysis of the  
16 Canadian Longitudinal Study on Aging. *Sleep* 2019;42(8).  
17
- 18  
19 7. Singareddy R, Vgontzas AN, Fernandez-Mendoza J, et al. Risk factors for incident  
20 chronic insomnia: A general population prospective study. *Sleep Med*  
21 2012;13(4):346–53.  
22
- 23  
24 8. Zhang Y, Ren R, Lei F, et al. Worldwide and regional prevalence rates of  
25 co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A  
26 systematic review and meta-analysis. *Sleep Med Rev* 2019;45:1–17.  
27
- 28  
29 9. Kessler RC, Berglund PA, Coulouvrat C, et al. Insomnia, comorbidity, and risk of  
30 injury among insured Americans: Results from the America Insomnia Survey. *Sleep*  
31 2012;35(6):825–34.  
32
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34 10. Kalmbach DA, Cheng P, Arnedt JT, et al. Improving daytime functioning, work  
35 performance, and quality of life in postmenopausal women with insomnia: comparing  
36 cognitive behavioral therapy for insomnia, sleep restriction therapy, and sleep hygiene  
37 education. *J Clin Sleep Med* 2019;15(7):999–1010.  
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40 11. Espie CA, Emsley R, Kyle SD et al. Effect of digital cognitive behavioral therapy for  
41 insomnia on health, psychological well-being, and sleep-related quality of life: a  
42 randomized clinical trial. *JAMA Psychiatry* 2019;76(1):21–30.  
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12. Thakral M, Von Korff M, McCurry SM, et al. Changes in dysfunctional beliefs about sleep after cognitive behavioral therapy for insomnia: A systematic literature review and meta-analysis. *Sleep Med Rev* 2020;49:101230.
13. Garland SN, Xie SX, DuHamel K, et al. Acupuncture versus cognitive behavioral therapy for insomnia in cancer survivors: a randomized clinical trial. *J Natl Cancer Inst* 2019;111(12):1323–31.
14. Liou KT, Root JC, Garland SN, et al. Effects of acupuncture versus cognitive behavioral therapy on cognitive function in cancer survivors with insomnia: A secondary analysis of a randomized clinical trial. *Cancer* 2020;126(13):3042–52.
15. Xing J, Wu X, Liu H, et al. Effects of electroacupuncture therapy and cognitive behavioral therapy in chronic insomnia: a randomized controlled study. *Evid Based Complement Alternat Med* 2020;5630130.
16. Liqian C, Jingwen R, Mingying Z, et al. Effects of acupuncture combined with cognitive behavioral therapy on sleep quality, sleep belief and attitude in patients with chronic insomnia. *Guangdong Medical Journal* 2020;41(10):1005–9.
17. Ruan JW, Wang CH, Liao XX, et al. Electroacupuncture treatment of chronic insomniacs. *Chin Med J* 2009;122(23):2869–73.
18. Freire AO, Sugai GC, Togeiro SM, et al. Immediate effect of acupuncture on the sleep pattern of patients with obstructive sleep apnoea. *Acupunct Med* 2010;28(3):115–9.
19. Gorban AN, Makarov VA, Tyukin IY. The unreasonable effectiveness of small neural ensembles in high-dimensional brain. *Phys Life Rev* 2019;29:55–88.
20. Bresch E, Großekathöfer U, Garcia-Molina G. Recurrent deep neural networks for real-time sleep stage classification from single channel EEG. *Front Comput Neurosci* 2018;12:85.
21. Hassan AR, Bhuiyan MIH. Automated identification of sleep states from EEG signals by means of ensemble empirical mode decomposition and random under sampling boosting. *Comput Methods Programs Biomed* 2017;140:201–10.

22. Schulz KF, Altman DG, Moher D: CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
23. MacPherson H, Altman DG, Hammerschlag R, et al. Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *J Evid Based Med* 2010;3(3):140–55.
24. Wang C, Yang WJ, Yu XT, et al. Acupuncture for insomnia with short sleep duration: protocol for a randomised controlled trial. *BMJ Open* 2020;10(3):e033731.
25. Battle DE. Diagnostic and Statistical Manual of Mental Disorders (DSM). *CoDAS* 2013;25(2):191–2.
26. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest* 2014;146(5):1387–94.
27. Qaseem A, Kansagara D, Forcica MA, et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2016;165(2):125–33.
28. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193–213.
29. Mollayeva T, Thurairajah P, Burton K, et al. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. *Sleep Med Rev* 2016;25:52–73.
30. Robinson BE, Kelley L: Concurrent validity of the Beck Depression Inventory as a measure of depression. *Psychol Rep* 1996;79(3 Pt 1):929–30.
31. Piotrowski C: Use of the Beck Depression Inventory in clinical practice. *Psychol Rep* 1996;79(3 Pt 1):873–4.
32. Carney CE, Ulmer C, Edinger JD, et al. Assessing depression symptoms in those with insomnia: an examination of the Beck depression inventory second edition (BDI-II). *J Psychiatr Res* 2009;43(5):576–82.

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4 33. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety:  
5 psychometric properties. *J Consult Clin Psychol* 1988;56(6):893–7.  
6  
7 34. Nyer M, Farabaugh A, Fehling K, et al. Relationship between sleep disturbance and  
8 depression, anxiety, and functioning in college students. *Depress Anxiety*  
9 2013;30(9):873–80.  
10  
11 35. Morin CM, Vallières A, Ivers H. Dysfunctional beliefs and attitudes about sleep  
12 (DBAS): Validation of a brief version (DBAS-16). *Sleep* 2007;30(11):1547–54.  
13  
14 36. Chung KF, Ho FY, Yeung WF. Psychometric comparison of the full and abbreviated  
15 versions of the dysfunctional beliefs and attitudes about sleep scale. *J Clin Sleep Med*  
16 2016;12(6):821–8.  
17  
18 37. Ramaswamy SM, Weerink MAS, Struys M, et al. Dexmedetomidine-induced deep  
19 sedation mimics non-rapid eye movement stage 3 sleep: Large-scale validation using  
20 machine learning. *Sleep* 2021;44(2).  
21  
22 38. Abou Jaoude M, Sun H, Pellerin KR, et al. Expert-level automated sleep staging of  
23 long-term scalp electroencephalography recordings using deep learning. *Sleep*  
24 2020;43(11).  
25  
26 39. Malhotra RK, Kirsch DB, Kristo DA, et al. Polysomnography for obstructive sleep  
27 apnea should include arousal-based scoring: An American Academy of Sleep Medicine  
28 position statement. *J Clin Sleep Med* 2018;14(7):1245–7.  
29  
30 40. Zhang P, Zhao Z. Interpretation of “Guidelines for the diagnosis and treatment of  
31 adult insomnia in China.” *Chin J Contemp Neurol Neurosurg* 2013;13(5):363–7.  
32  
33 41. Wilt TJ, MacDonald R, Brasure M, et al. Pharmacologic treatment of insomnia  
34 disorder: An evidence report for a clinical practice guideline by the American College of  
35 Physicians. *Ann Intern Med* 2016;165(2):103–12.  
36  
37 42. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and  
38 treatment of insomnia. *J Sleep Res* 2017;26(6):675–700.  
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4 43. Kathol RG, Arnedt JT. Cognitive behavioral therapy for chronic insomnia:  
5 Confronting the challenges to implementation. *Ann Intern Med* 2016;165(2):149–50.  
6  
7 44. Ree M, Junge M, Cunnington D. Australasian Sleep Association position statement  
8 regarding the use of psychological/behavioral treatments in the management of insomnia  
9 in adults. *Sleep Med* 2017;Suppl 36(1):S43–7.  
10  
11 45. Coutaux A. Non-pharmacological treatments for pain relief: TENS and acupuncture.  
12 *Joint bone spine* 2017;84(6):657–61.  
13  
14 46. Iravani S, Kazemi Motlagh AH, Emami Razavi SZ, et al. Effectiveness of acupuncture  
15 treatment on chemotherapy-induced peripheral neuropathy: A pilot, randomized,  
16 assessor-blinded, controlled trial. *Pain Res Manag* 2020;2504674.  
17  
18 47. Zhang L, Fabbri D, Upender R, et al. Automated sleep stage scoring of the Sleep  
19 Heart Health Study using deep neural networks. *Sleep* 2019;42(11).  
20  
21 48. Kempfner J, Sorensen GL, Sorensen HB, et al. Automatic REM sleep detection  
22 associated with idiopathic rem sleep Behavior Disorder. Annual International Conference  
23 of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine  
24 and Biology Society Annual International Conference 2011:6063-6066.  
25  
26 49. Lajnef T, Chaibi S, Ruby P, et al. Learning machines and sleeping brains: Automatic  
27 sleep stage classification using decision-tree multi-class support vector machines. *Journal*  
28 *of neuroscience methods* 2015;250:94-105.  
29  
30 50. Qu W, Wang Z, Hong H, et al. A Residual Based Attention Model for EEG Based  
31 Sleep Staging. *IEEE journal of biomedical and health informatics*  
32 2020;24(10):2833-2843.  
33  
34 51. Wang Y, Loparo KA, Kelly MR, et al. Evaluation of an automated single-channel  
35 sleep staging algorithm. *Nature and science of sleep* 2015;7:101-111.  
36  
37 52. Stepnowsky C, Levendowski D, Popovic D, et al. Scoring accuracy of automated  
38 sleep staging from a bipolar electroocular recording compared to manual scoring by  
39 multiple raters. *Sleep medicine* 2013; 14(11):1199-1207.  
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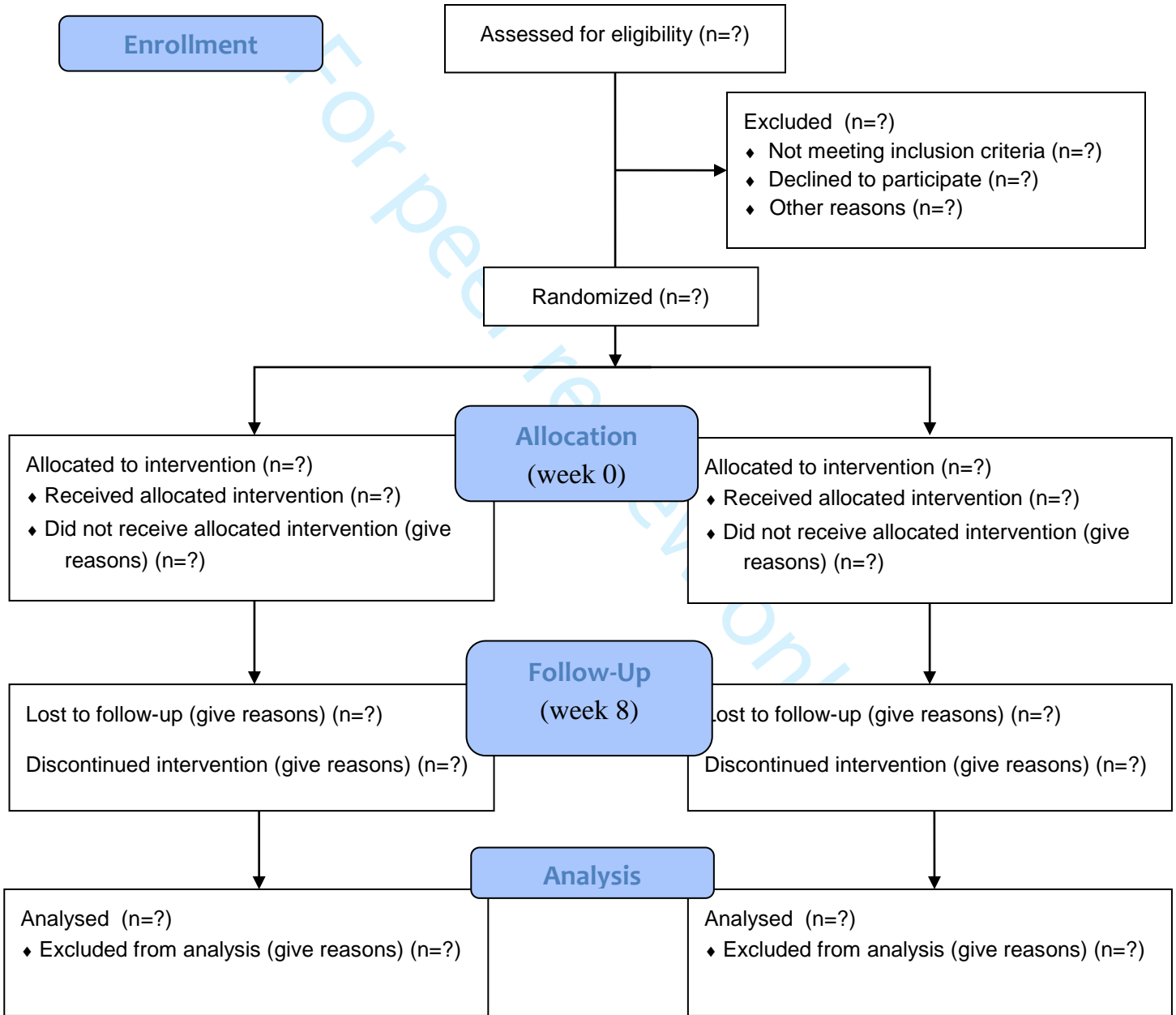
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Fig 1. CONSORT 2010 Flow Diagram

For peer review only



**CONSORT 2010 Flow Diagram**







STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | <u>1</u>                 |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | <u>1</u>                 |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | <u>1</u>                 |
| Protocol version                  | 3       | Date and version identifier  | <u>1</u>                 |
| Funding                           | 4       | Sources and types of financial, material, and other support  | <u>12</u>                |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | <u>1,12</u>              |
|                                   | 5b      | Name and contact information for the trial sponsor   | <u>12</u>                |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | <u>12</u>                |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | <u>NA</u>                |

## 1 Introduction

|    |                |    |   |            |
|----|----------------|----|---|------------|
| 2  |                |    |   |            |
| 3  | Background and | 6a | Description of research question and justification for undertaking the trial, including summary of    | <u>3-4</u> |
| 4  | rationale      |    | relevant studies (published and unpublished) examining benefits and harms for each intervention       |            |
| 5  |                |    |   |            |
| 6  |                | 6b | Explanation for choice of comparators   | <u>5</u>   |
| 7  |                |    |   |            |
| 8  | Objectives     | 7  | Specific objectives or hypotheses   | <u>4</u>   |
| 9  |                |    |   |            |
| 10 | Trial design   | 8  | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single |            |
| 11 |                |    | group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)   | <u>4</u>   |
| 12 |                |    |   |            |
| 13 |                |    |   |            |

## 14 Methods: Participants, interventions, and outcomes

|    |                      |     |  |                           |
|----|----------------------|-----|--|---------------------------|
| 15 |                      |     |  |                           |
| 16 | Study setting        | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where      | <u>4-5</u>                |
| 17 |                      |     | data will be collected. Reference to where list of study sites can be obtained                           |                           |
| 18 |                      |     |  |                           |
| 19 | Eligibility criteria | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres | <u>6</u>                  |
| 20 |                      |     | and individuals who will perform the interventions (eg, surgeons, psychotherapists)                      |                           |
| 21 |                      |     |  |                           |
| 22 | Interventions        | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they    | <u>6-7</u>                |
| 23 |                      |     | will be administered   |                           |
| 24 |                      |     |  |                           |
| 25 |                      | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug  | <u>6</u>                  |
| 26 |                      |     | dose change in response to harms, participant request, or improving/worsening disease)                   |                           |
| 27 |                      |     |  |                           |
| 28 |                      | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring             | <u>6</u>                  |
| 29 |                      |     | adherence (eg, drug tablet return, laboratory tests)   |                           |
| 30 |                      |     |  |                           |
| 31 |                      | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial            | <u>6</u>                  |
| 32 |                      |     |  |                           |
| 33 | Outcomes             | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg,                 | <u>7-9</u>                |
| 34 |                      |     | systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event),        |                           |
| 35 |                      |     | method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of          |                           |
| 36 |                      |     | the clinical relevance of chosen efficacy and harm outcomes is strongly recommended                      |                           |
| 37 |                      |     |  |                           |
| 38 | Participant timeline | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments,             | <u>4,Table 1,Figure 1</u> |
| 39 |                      |     | and visits for participants. A schematic diagram is highly recommended (see Figure)                      |                           |
| 40 |                      |     |  |                           |
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|----|---|-----|--|------------|
| 1  | Sample size   | 14  | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations  |            |
| 2  |   |     |  |            |
| 3  |   |     |  |            |
| 4  | Recruitment   | 15  | Strategies for achieving adequate participant enrolment to reach target sample size  | <u>8-9</u> |
| 5  |   |     |  |            |
| 6  |   |     |  |            |
| 7  | <b>Methods: Assignment of interventions (for controlled trials)</b> |     |  |            |
| 8  | Allocation:   |     |  | <u>5</u>   |
| 9  |   |     |  |            |
| 10 | Sequence  | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions   | <u>5</u>   |
| 11 | generation  |     |  |            |
| 12 |   |     |  |            |
| 13 |   |     |  |            |
| 14 |   |     |  |            |
| 15 |   |     |  |            |
| 16 | Allocation  | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  | <u>5</u>   |
| 17 | concealment   |     |  |            |
| 18 | mechanism   |     |  |            |
| 19 |   |     |  |            |
| 20 | Implementation  | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | <u>5</u>   |
| 21 |   |     |  |            |
| 22 |   |     |  |            |
| 23 |   |     |  |            |
| 24 | Blinding (masking)  | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | <u>5</u>   |
| 25 |   |     |  |            |
| 26 |   |     |  |            |
| 27 |   | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | <u>5</u>   |
| 28 |   |     |  |            |
| 29 |   |     |  |            |
| 30 |   |     |  |            |
| 31 | <b>Methods: Data collection, management, and analysis</b>           |     |  |            |
| 32 |   |     |  |            |
| 33 | Data collection   | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | <u>9</u>   |
| 34 | methods   |     |  |            |
| 35 |   |     |  |            |
| 36 |   |     |  |            |
| 37 |   |     |  |            |
| 38 |   |     |  |            |
| 39 |   |     |  |            |
| 40 |   | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  | <u>9</u>   |
| 41 |   |     |  |            |
| 42 |   |     |  |            |
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|----|---------------------------------|-----|---|-------------|
| 1  | Data management                 | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol   | <u>9-10</u> |
| 2  |                                 |     |   |             |
| 3  |                                 |     |   |             |
| 4  |                                 |     |   |             |
| 5  | Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | <u>9-10</u> |
| 6  |                                 |     |   |             |
| 7  |                                 |     |   |             |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | <u>9-19</u> |
| 9  |                                 |     |   |             |
| 10 |                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | <u>9-10</u> |
| 11 |                                 |     |   |             |
| 12 |                                 |     |   |             |
| 13 |                                 |     |   |             |
| 14 | <b>Methods: Monitoring</b>      |     |   |             |
| 15 |                                 |     |   |             |
| 16 | Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | <u>9-10</u> |
| 17 |                                 |     |   |             |
| 18 |                                 |     |   |             |
| 19 |                                 |     |   |             |
| 20 |                                 |     |   |             |
| 21 |                                 |     |   |             |
| 22 |                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | <u>9-10</u> |
| 23 |                                 |     |   |             |
| 24 |                                 |     |   |             |
| 25 | Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | <u>9-10</u> |
| 26 |                                 |     |   |             |
| 27 |                                 |     |   |             |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | <u>9-10</u> |
| 29 |                                 |     |   |             |
| 30 |                                 |     |   |             |
| 31 |                                 |     |   |             |
| 32 | <b>Ethics and dissemination</b> |     |   |             |
| 33 |                                 |     |   |             |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | <u>5</u>    |
| 35 |                                 |     |   |             |
| 36 |                                 |     |   |             |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | <u>NA</u>   |
| 38 |                                 |     |   |             |
| 39 |                                 |     |   |             |
| 40 |                                 |     |   |             |
| 41 |                                 |     |   |             |
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|----|-------------------------------|-----|--|---|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)   | 6                                       |
| 2  |                               |     |  |   |
| 3  |                               |     |  |   |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable  | 6                                       |
| 5  |                               |     |  |   |
| 6  |                               |     |  |   |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial   | 6                                       |
| 8  |                               |     |  |   |
| 9  |                               |     |  |   |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site  | 12                                      |
| 11 |                               |     |  |   |
| 12 |                               |     |  |   |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators  | 6                                       |
| 14 |                               |     |  |   |
| 15 |                               |     |  |   |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  | 6                                       |
| 17 |                               |     |  |   |
| 18 |                               |     |  |   |
| 19 |                               |     |  |   |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 6                                       |
| 21 |                               |     |  |   |
| 22 |                               |     |  |   |
| 23 |                               |     |  |   |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers   | 6                                       |
| 25 |                               |     |  |   |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code  | 6                                       |
| 27 |                               |     |  |   |
| 28 |                               |     |  |   |
| 29 |                               |     |  |   |
| 30 | <b>Appendices</b>             |     |  |   |
| 31 |                               |     |  |   |
| 32 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates   | <u>See The Ethics Approval Document</u> |
| 33 |                               |     |  |   |
| 34 |                               |     |  |   |
| 35 |                               |     |  |   |
| 36 |                               |     |  |   |
| 37 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable   | <u>NA</u>                               |
| 38 |                               |     |  |   |
| 39 |                               |     |  |   |

1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
2 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
3 [“Attribution-NonCommercial-NoDerivs 3.0 Unported”](#) license.  
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# BMJ Open

## Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

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|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2022-063442.R1   |
| Article Type:                   | Protocol   |
| Date Submitted by the Author:   | 16-Oct-2022  |
| Complete List of Authors:       | Pei, Wenya; Sun Yat-sen University First Affiliated Hospital<br>He, Te; South China University of Technology<br>Yang, Pei; South China University of Technology<br>Lv, Xiaozhou; Sun Yat-sen University First Affiliated Hospital<br>Jiao, Boyu; Sun Yat-sen University First Affiliated Hospital<br>Meng, Fanqi; Sun Yat-sen University First Affiliated Hospital<br>Yan, Yingshuo; Sun Yat-sen University First Affiliated Hospital<br>Cui, Liqian; Sun Yat-sen University First Affiliated Hospital<br>He, Guanheng; Sun Yat-sen University First Affiliated Hospital<br>Zhou, Xin; Sun Yat-sen University First Affiliated Hospital<br>Wen, Guihua; South China University of Technology<br>Ruan, Jingwen; Sun Yat-sen University First Affiliated Hospital,<br>Lu, Liming; Guangzhou University of Chinese Medicine |
| <b>Primary Subject Heading</b>: | Complementary medicine   |
| Secondary Subject Heading:      | Health services research, Neurology, Public health   |
| Keywords:                       | CLINICAL PHYSIOLOGY, Rehabilitation medicine < INTERNAL MEDICINE, COMPLEMENTARY MEDICINE, REHABILITATION MEDICINE  |
|                                 |  |

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Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in  
patients with insomnia: study protocol for a randomized controlled trial

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## Abstract

### Introduction

Insomnia affects physical and mental health due to the lack of continuous and complete sleep architecture. Polysomnograms (PSGs) are used to record electrical information to perform sleep architecture using deep learning. Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) could not only improve sleep quality, solve anxiety, depression but also ameliorate poor sleep habits and detrimental cognition. However, the mechanism of clinical study in this process remain unclear.

### Methods and analysis

This randomized controlled trial will evaluate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia. Participants will be randomized to receive either electroacupuncture combined with CBT-I or sham acupuncture and followed up for four weeks. The primary outcome is sleep quality, which is evaluated by the Pittsburgh sleep quality index(PSQI). The secondary outcome measures include a measurement of depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events. Sleep architecture will be assessed using deep learning on PSGs.

### Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals.

### Trial registration number

CTR2100052502

**Keywords:** insomnia, cognitive behavioral therapy for insomnia, electroacupuncture, randomized controlled trial

### Strengths and limitations of this study

- This study will investigate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia.
- A randomized controlled trial will be conducted to assess sleep quality, depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events.
- Deep learning will be used to observe the effects of electroacupuncture combined with CBT-I on sleep architecture in different dimensions.
- Using deep learning, this study will develop a high-performing, reference channel-free, automated sleep staging algorithm to analyze the sleep architecture.
- We will provide an insight into the combined application of electroacupuncture and CBT-I for insomnia in the clinic

## Introduction

Insomnia is characterized by difficulties in initiating or maintaining sleep or impaired daytime functioning, which impact both physical and mental health<sup>[1-3]</sup>. The lack of continuous and complete sleep architecture due to long-term fragmented and light sleep in patients with insomnia causes a decrease in sleep quality, which affects daily functions, and even induces anxiety, depression, and other mental symptoms<sup>[4-6]</sup>. With the increasing pressures in daily life and work, insomnia is becoming a public health problem that needs to be solved urgently as it worsens the quality of life of patients, burdens caregivers, and increases social and economic costs<sup>[7-9]</sup>.

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for insomnia and may improve sleep quality and alleviate poor sleep cognition in patients with insomnia<sup>[10-12]</sup>. During the early stage of treatment, the sleep quality of patients with severe anxiety were improved slowly and the compliance of these patients were poor. Thus, as confirmed in previous studies, acupuncture combined with CBT-I could not only solve anxiety, depression, and other emotions caused by insomnia but also ameliorate poor sleep habits and detrimental cognition<sup>[13-16]</sup>.

However, there is a lack of rigorous clinical evidence on the treatment of insomnia with acupuncture combined with CBT-I; moreover, the clinical mechanism is unclear. In previous studies, we found that by analyzing polysomnograms(PSGs), electroacupuncture improves sleep architecture and prolongs the duration of slow-wave and rapid-eye-movement (REM) sleep<sup>[17-19]</sup>. But whether acupuncture combined with CBT-I improves sleep architecture requires further research.

During the past decade, the application of deep learning to automatic sleep staging using PSGs has shown promise for understanding the macrostructure of sleep. Deep learning allows the automatic extraction of features from data related to classification tasks, and the performance of deep neural networks continues to improve as the size of the dataset increases<sup>[20-22]</sup>.

Using a high-performance automatic sleep staging algorithm to analyze PSGs recordings via deep learning, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. Furthermore, this research will provide guidance for electroacupuncture combined with CBT-I using artificial intelligence.

## Methods

### Study design

The study will be an assessor-blinded, randomized controlled trial. The protocol was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). We will follow the Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines for the design and reporting of the trial<sup>[23, 24]</sup>. The flowchart of the trial is presented in Figure 1, and the schedule of enrolment, interventions, and outcome assessments are presented in Table 1.

Sample size calculations: Referring to the previous literature<sup>[25]</sup>, we assume that the expected PSQI value and determine that an alpha level of 0.05, which would allow us to detect a difference in PSQI score between the two groups. Allowing for a 15% dropout rate, a sample size of 36 in each group is sufficient to meet statistical requirements.

### Randomization, allocation, and blinding

Patients who are interested in participating in the trial will initially be screened by phone and then asked to participate in a face-to-face interview to conduct further surveys. After recruiting all participants, random numbers will be generated and assigned by a central randomization system of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. The researcher who will screen the eligible patients after baseline

Table 1 Research flow chart

| Project                              | Screening                     | Observation phase            |                            |                            | Follow-up phase            |                     |
|--------------------------------------|-------------------------------|------------------------------|----------------------------|----------------------------|----------------------------|---------------------|
|                                      | assessment 0<br>pre-treatment | Assession 1<br>pre-treatment | Assession 2<br>Week 2±1day | Assession 3<br>Week 4±2day | Assession 4<br>Week 8±2day | Unplanned follow-up |
| Medical history collection           | √                             | -                            | -                          | -                          | -                          |                     |
| Sign the informed consent form       | √                             | -                            | -                          | -                          | -                          |                     |
| Inclusion criteria                   | √                             | -                            | -                          | -                          | -                          |                     |
| Exclusion criteria                   | √                             | -                            | -                          | -                          | -                          |                     |
| Basic Information                    | √                             | -                            | -                          | -                          | -                          |                     |
| Vital signs                          | √                             | √                            | √                          | √                          | √                          | ※                   |
| Index of laboratory inspection       | ※                             | ※                            | ※                          | ※                          | ※                          |                     |
| PSG                                  | -                             | √                            | -                          | √                          | -                          |                     |
| Pittsburgh sleep quality index(PSQI) | -                             | √                            | √                          | √                          | √                          |                     |
| Beck depression inventory(BDI)       | -                             | √                            | √                          | √                          | √                          |                     |
| Beck anxiety inventory(BAI)          | -                             | √                            | √                          | √                          | √                          |                     |
| DBAS-16                              | -                             | √                            | √                          | √                          | √                          |                     |
| Adverse Events                       | -                             | ※                            | ※                          | ※                          | ※                          | ※                   |
| Medication records                   | -                             | √                            | √                          | √                          | √                          |                     |
| Terminate test evaluation            | -                             | ※                            | ※                          | ※                          | ※                          |                     |

Notes: “※”Record when necessary; PSG: Long-term scalp electroencephalogram recording; DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep Scale 16 versio

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4 will assign patients to either the treatment or control group. Researchers, which include  
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6 statisticians, outcome assessors, and data analysts, will all be blinded to patients' group  
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8 assignments. Although acupuncturists will be not blinded to group assignment, they will  
9  
10 not be involved in outcome assessments or data analyses. In addition, all researchers will  
11  
12 undergo training for specific procedures before the trial begins.

### 13 **Participants and recruitment**

14  
15 Patients will be recruited using hospital-based advertisements in the Department of  
16  
17 Acupuncture and Department of Neurology of the First Affiliated Hospital of Sun  
18  
19 Yat-sen University from January 1,2022 to December 30,2025.

20  
21 The inclusion criteria will be as follows: (1) meets diagnostic criteria for insomnia  
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23 based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition<sup>[26]</sup>  
24  
25 and the International Classification of Sleep Disorders, Third Edition<sup>[27]</sup>, (2) aged 18–65  
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27 years, (3) experienced insomnia for more than 1 month but less than 2 years before the  
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29 start of the trial, (4) voluntarily agrees to participate in the investigation and provides  
30  
31 written informed consent before the clinical trial starts.

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33 The exclusion criteria will be as follows: (1) serious cardiovascular, liver, kidney, or  
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35 hematopoietic system disease, (2) insomnia was caused by a nervous system disease (e.g.,  
36  
37 stroke or Parkinson's disease), (3) insomnia was caused by a mental disorder, such as  
38  
39 depression or anxiety, (4) history of sleep apnea, (5) pregnant or lactating women, (6)  
40  
41 have received or currently receiving CBT-I.

42  
43 Withdrawal criteria will be as follows: (1) patient withdrawal from the trial because  
44  
45 of personal reasons, (2) patient has an adverse reaction related to acupuncture and refuses  
46  
47 to continue treatment, (3) during the follow-up period, the patient cannot be contacted  
48  
49 because of change of address and telephone number.

### 50 **Intervention**

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52 The intervention will begin the day following randomization. All participants will receive  
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54 20 times treatments (five times per week for 4 weeks).  
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## Observation group

### Acupuncture treatment

Patients' skin will be disinfected with 75% alcohol, and patients will be asked to lie supine and wear eye masks for a better curative effect. Each participant will receive acupuncture treatment from the same acupuncturist who has more than 5 years of clinical experience in acupuncture therapy. The temperature of the treatment room will not be lower than 25°C.

Patients in the acupuncture group will receive electroacupuncture treatment on Sishenchong (EX-HN1), bilateral Neiguan (PC6), bilateral Taixi (KI3), bilateral Shenmen (HT7), and bilateral Sanyinjiao (SP6)<sup>[16]</sup>. Tube-guided acupuncture needles will be inserted to a depth of 17-25 mm at each acupoint (acupuncture location and method for each acupoint are provided in Table 2 and Figure 2). A low-frequency electronic pulse therapy instrument (G6805-2A, Shanghai Huayi Medical Instrument Co, Shanghai, China) will be used with 10-Hz continuous waves, and the current will range from 1 to 5 mA which will be adjusted based on the tolerance of each patient.

### CBT-I treatment

CBT-I will be given while acupuncture treatment is in progress. The intervention will consist of behavioral components (e.g. sleep restriction and stimulus control), cognitive components (e.g., cognitive restructuring and paradoxical intention), progressive muscle relaxation, and sleep hygiene<sup>[28]</sup>.

## Control group

The procedure for the control group will be the same as that for the observation group with no CBT-I treatment. The major difference in interventions between the two groups being the tube needling method, in which no needle will be inserted through the tube for patients in the control group. To mimic the sensation of a real needle being inserted into the body, the acupuncturist will place the tube close to the skin at the acupoint and tap the top of the tube.

## Quality control

The trial will be conducted under the supervision of the First Affiliated Hospital of Sun Yat-sun University. A qualified clinical trial expert will be invited to monitor the study to identify problems during the trial, examine collected data, and control bias.

## Outcome measures

### Primary outcome

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is an internationally established tool that is used to evaluate sleep quality. The scale includes seven dimensions that consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication, and daytime dysfunction. The score correlates adversely with sleep quality which a higher score means the sleep quality is worse, and each factor has a score of 0 to 3 to provide a total score of 21 points<sup>[29, 30]</sup>.

### Secondary outcomes

#### The Beck depression inventory

The Beck depression inventory (BDI) is a valid self-assessment index to measure depression severity and consists of 13 items. Each item is scored from 0 to 3 (0 to 4 indicates no depression, 5 to 7 indicates mild depression, 8 to 15 indicates moderate depression), with a score of 16 points or more considered as severe depression<sup>[31-33]</sup>.

#### The Beck anxiety inventory

The Beck anxiety inventory (BAI) is used to assess the degree of anxiety and consists of 21 items scored from 1 to 4 (15 to 25 points indicates mild anxiety, 26 to 35 points indicates moderate anxiety, and 36 points is considered severe anxiety)<sup>[34, 35]</sup>.

### Other Outcomes

#### The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version (DBAS-16) is used to evaluate maladaptive cognitions associated with sleep. There are 16 items in the index,



Table 2 Acupuncture location and method for each acupoint

| Acupoint             | Location   | Needling method  |
|----------------------|--|--|
| Sishenchong (EX-HN1) | On the parietal region, 1 cun anterior, posterior and lateral to Baihui, 4 acupoints totally.  | The angle between the needle tip and the scalp is 30°. Move the needle tip backward along the anteriore posterior midline, and then insert the needle 0.5 cun. |
| Neiguan(PC6)         | On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist. | Puncture perpendicularly 1-1.5 cun.  |
| Taixi (KI3)          | In the depression between the tip of the medial malleolus and the Achilles tendon.   | Puncture perpendicularly 0.5-1 cun.  |
| Shenmen (HT7)        | On the palmar ulnar end of the transverse crease of the wrist, and on the radial aspect of the tendon of the ulnar flexor m. of the wrist.             | Puncture perpendicularly 0.5-1 cun.  |
| Sanyinjiao (SP6)     | Posterior to the mesial border of the tibia, and 3 cun above the tip of the medial malleolus   | Puncture perpendicularly 1-1.5 cun.  |

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4 which are divided into four factors comprising consequences of insomnia, worry about  
5 sleep, sleep expectations, and medication. These factors are scored on a scale of  
6 1-5 (strongly disagree to strongly agree). The total score is positively correlated with the  
7 reasonableness of sleep beliefs and attitudes<sup>[36, 37]</sup>.  
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### 10 11 **Sleep staging**

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13 The PARADISEP&D9600 (U.S.) Polysomnography Monitoring and Analysis System  
14 will be used to simultaneously monitor EEG, EOG, and EMG. A large clinical dataset of  
15 PSG recordings will be used to train a hybrid convolutional neural network (CNN) and  
16 recurrent neural network (RNN) to learn effective and generalizable features for sleep  
17 stage scoring<sup>[38, 39]</sup>. Then clinical data will be used to identify the deep learning  
18 algorithm. Sleep staging for both datasets will be performed by expert sleep technicians  
19 in nonoverlapping 30-s epochs according to standards by the American Academy of  
20 Sleep Medicine (AASM), as one of five stages: wake (W), non-rapid eye movement (REM)  
21 stage 1 (N1), non-REM stage 2 (N2), non-REM stage 3 (N3), and rapid eye  
22 movement (REM)<sup>[40]</sup>.  
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### 33 **Adverse events**

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35 During treatment and four weeks after treatment, a questionnaire will be administered to  
36 evaluate the various discomforts that may be caused by acupuncture: hangover, addiction,  
37 tolerance, fatigue after waking, insomnia rebound, daytime alertness, cognitive function,  
38 and behavior ability.  
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### 42 **Patients and public involvement**

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44 Patients and the public are not involved in the design or conduct of the study or the  
45 outcome measures, and no attempt will be made to assess the burden of the intervention  
46 on the patients themselves. The results of this study will be disseminated to study  
47 participants via the website of our hospitals.  
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### 52 **Statistical analysis**

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4 All analyses will be performed on the intention-to-treat population of participants who  
5 had at least one treatment. Missing data will be replaced according to the principle of the  
6 last observation carried forward. Data analyses will be performed using the SPSS version  
7 25 (IBM Corp.) software. All available data will be analyzed descriptively. For  
8 continuous data, the normality test will be applied at the beginning of the analysis.  
9  
10 Results will be presented as means, standard deviations, and 95% confidence intervals  
11 (CIs) for continuous data that conform to the normal distribution and medians, quartiles,  
12 and ranges for rank data and continuous data that are not normally distributed. Discrete  
13 data will be presented as percentages.  
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16  
17 We will first examine the descriptive data for sample characteristics at baseline, and  
18 independent samples t-tests will be used to compare groups for continuous variables,  
19 whereas chi-square analysis will be used to compare groups for dichotomous variables.  
20  
21 Second, we will perform two series of repeated-measures and univariate analyses of  
22 covariance (ANCOVA) models to examine treatment effects. We will use  
23 repeated-measures ANCOVAs to analyze the primary and secondary outcome measures  
24 (i.e., PSQI, BDI, BAI, DBAS-16, and sleep staging scores) from pre-treatment to  
25 post-treatment. If a significant effect is observed, we will conduct posthoc paired samples  
26 t-tests to examine within-group changes in study outcomes. For all study outcomes, we  
27 will then perform univariate ANCOVAs to test for group differences in post-treatment  
28 values while controlling for relevant covariates. This process will be repeated to examine  
29 changes in study outcomes from pretreatment to postnatal follow-up.  
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33 When necessary, ITT analysis and sensitivity analysis will be used to assess the  
34 robustness of the conclusions of the entire clinical trial. To evaluate the consistency of the  
35 trial and explore the factors that affect efficacy or prognosis, subgroup analysis will be  
36 conducted to identify the population with better efficacy. Safety analysis will be used to  
37 assess the incidence of adverse events and related symptoms in patients with insomnia  
38 during treatment and follow-up.  
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## Discussion

Currently, the main treatments recommended for insomnia are non-pharmaceutical and pharmaceutical treatments. Pharmaceutical treatments include benzodiazepines as well as new non-benzodiazepine drugs, which can shorten the latency to fall asleep and prolong total sleep time but also affect normal sleep physiology and cause adverse reactions<sup>[41, 42]</sup>. CBT-I, which is recommended as a first-line treatment for insomnia by the European insomnia guidelines, is limited in clinical practice because of insufficient professional therapists and poor compliance of patients with insomnia, especially in developing countries such as China<sup>[42-45]</sup>.

As a complementary alternative therapy with a long history in China, acupuncture has been used as a clinical treatment for insomnia with fewer adverse effects and less permanent damage. Previous studies showed that either acupuncture or CBT-I could produce clinically meaningful improvements in insomnia symptoms, and our preliminary research have confirmed that acupuncture combined with CBT-I also alleviate not only insomnia symptoms but also negative emotions such as anxiety and depression<sup>[13, 14, 16]</sup>. But whether acupuncture combined with CBT-I could influence sleep habits and correct cognition, and what the clinic clinical mechanism worth further research.

To ameliorate sleep habits, correct cognition, and alleviate anxiety, depression, and other emotions caused by insomnia, this study will use electroacupuncture combined with CBT-I and observe sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. In this study, PSQI will be used to assess the sleep quality, BDI and BAI will be used to evaluate the depression severity and anxiety. At the same time, we will use DBAS-16 to evaluate the sleep beliefs and attitudes before and after treatment. Because of the particularity of acupuncture therapy, the implementation of blinding is difficult in clinical research<sup>[46, 47]</sup>. A research team composed of researchers, therapists, testers, and statisticians will be established to reduce any bias that may occur

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4 during the research process by blinding testers and statisticians. This study will provide  
5 clinical evidence for the effect and safety of electroacupuncture combined with CBT-I  
6 and provide a decision-making reference for clinicians, patients, and policymakers.  
7

8  
9 To analyze the effects of electroacupuncture combined with CBT-I on sleep  
10 architecture and sleep quality in patients with insomnia, deep learning will be used to  
11 analyze PSGs in various clinical settings in this study. PSGs are used widely for clinical  
12 evaluation because they are more sensitive than routine EEGs (typically 30–60 min  
13 duration) in capturing paroxysmal electrical abnormalities<sup>[48, 49]</sup>. During the past decade,  
14 there have been various advances in automated sleep staging of PSGs data using the  
15 ability of deep learning methods to automatically extract features from data that are  
16 relevant to the classification; moreover, the performance of deep neural networks  
17 continues to improve as datasets become larger<sup>[50-52]</sup>. Using deep learning, this study will  
18 develop a high-performing, reference channel-free, automated sleep staging algorithm to  
19 analyze the sleep architecture which will provide a clinical mechanism in artificial  
20 intelligence.  
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23 In summary, this study will use electroacupuncture combined with CBT-I to treat  
24 insomnia and observe the sleep beliefs and attitudes of patients with insomnia in different  
25 dimensions using deep learning. Moreover, we will provide a solid research basis for the  
26 combined application of electroacupuncture and CBT-I for insomnia in the clinic.  
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#### 29 Acknowledgments

30 Not applicable.  
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#### 33 Footnotes

34 Contributors: Wenya Pei and Te He designed the trial protocol and drafted the manuscript.  
35 Liming Lu, Jingwen Ruan, and Guihua Wen revised the manuscript. Pei Yang, Xiaozhou  
36 Lv, and Boyu Jiao will plan the data analysis. Liqian Cui, Yingshuo Yan, Fanqi Meng,  
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4 Guanheng He, and Xin Zhou will participate in participant recruitment. All authors  
5 discussed, read, and revised the manuscript, and all approved the publication of this  
6 protocol.  
7

8  
9 Funding: The study was supported by the Key R&D Program of Guangdong Province  
10 (2020B1111120001).  
11

12  
13 Competing interests: None declared.  
14

15 Patient consent for publication: Not applicable  
16

17 Provenance and peer review: Not commissioned; externally peer-reviewed.  
18

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21 Ethics and dissemination: The study was approved by the ethics committee of the First  
22 Affiliated Hospital of Sun Yat-sun University (2021763). Participants will be included  
23 only after they provide written informed consent. The study was registered in the Chinese  
24 Clinical Trial Registry (No.ChiCTR2100052502, 30/10/2021).  
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31 Ethics statements

32 Patient consent for publication

33 Not applicable.  
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39 References

- 40  
41 1. Riemann D, Benz F, Dressle RJ, Espie CA, Johann AF, Blanken TF, Leerssen J,  
42 Wassing R, Henry AL, Kyle SD *et al*: Insomnia disorder: State of the science and  
43 challenges for the future. *Journal of sleep research* 2022, 31(4):e13604.  
44  
45 2. Chan WS, Levsen MP, McCrae CS: A meta-analysis of associations between obesity  
46 and insomnia diagnosis and symptoms. *Sleep medicine reviews* 2018, 40:170-182.  
47  
48 3. Wickwire EM: The Value of Digital Insomnia Therapeutics: What We Know and  
49 What We Need To Know. *Journal of clinical sleep medicine : JCSM : official publication*  
50 *of the American Academy of Sleep Medicine* 2019, 15(1):11-13.  
51  
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57  
58  
59  
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4. Kalmbach DA, Anderson JR, Drake CL: The impact of stress on sleep: Pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. *Journal of sleep research* 2018, 27(6):e12710.
5. Shekleton JA, Flynn-Evans EE, Miller B, Epstein LJ, Kirsch D, Brogna LA, Burke LM, Bremer E, Murray JM, Gehrman P *et al*: Neurobehavioral performance impairment in insomnia: relationships with self-reported sleep and daytime functioning. *Sleep* 2014, 37(1):107-116.
6. Cross NE, Carrier J, Postuma RB, Gosselin N, Kakinami L, Thompson C, Chouchou F, Dang-Vu TT: Association between insomnia disorder and cognitive function in middle-aged and older adults: a cross-sectional analysis of the Canadian Longitudinal Study on Aging. *Sleep* 2019, 42(8).
7. Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML, Bixler EO: Risk factors for incident chronic insomnia: a general population prospective study. *Sleep medicine* 2012, 13(4):346-353.
8. Zhang Y, Ren R, Lei F, Zhou J, Zhang J, Wing YK, Sanford LD, Tang X: Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A systematic review and meta-analysis. *Sleep medicine reviews* 2019, 45:1-17.
9. Kessler RC, Berglund PA, Coulouvrat C, Fitzgerald T, Hajak G, Roth T, Shahly V, Shillington AC, Stephenson JJ, Walsh JK: Insomnia, comorbidity, and risk of injury among insured Americans: results from the America Insomnia Survey. *Sleep* 2012, 35(6):825-834.
10. Kalmbach DA, Cheng P, Arnedt JT, Cuamatzi-Castelan A, Atkinson RL, Fellman-Couture C, Roehrs T, Drake CL: Improving Daytime Functioning, Work Performance, and Quality of Life in Postmenopausal Women With Insomnia: Comparing Cognitive Behavioral Therapy for Insomnia, Sleep Restriction Therapy, and Sleep



Hygiene Education. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2019, 15(7):999-1010.

11. Espie CA, Emsley R, Kyle SD, Gordon C, Drake CL, Siriwardena AN, Cape J, Ong JC, Sheaves B, Foster R *et al*: Effect of Digital Cognitive Behavioral Therapy for Insomnia on Health, Psychological Well-being, and Sleep-Related Quality of Life: A Randomized Clinical Trial. *JAMA psychiatry* 2019, 76(1):21-30.

12. Thakral M, Von Korff M, McCurry SM, Morin CM, Vitiello MV: Changes in dysfunctional beliefs about sleep after cognitive behavioral therapy for insomnia: A systematic literature review and meta-analysis. *Sleep medicine reviews* 2020, 49:101230.

13. Garland SN, Xie SX, DuHamel K, Bao T, Li Q, Barg FK, Song S, Kantoff P, Gehrman P, Mao JJ: Acupuncture Versus Cognitive Behavioral Therapy for Insomnia in Cancer Survivors: A Randomized Clinical Trial. *Journal of the National Cancer Institute* 2019, 111(12):1323-1331.

14. Liou KT, Root JC, Garland SN, Green J, Li Y, Li QS, Kantoff PW, Ahles TA, Mao JJ: Effects of acupuncture versus cognitive behavioral therapy on cognitive function in cancer survivors with insomnia: A secondary analysis of a randomized clinical trial. *Cancer* 2020, 126(13):3042-3052.

15. Xing J, Wu X, Liu H, Wang J, Jiang S, Lozada A, Wang Y: Effects of Electroacupuncture Therapy and Cognitive Behavioral Therapy in Chronic Insomnia: A Randomized Controlled Study. *Evidence-based complementary and alternative medicine : eCAM* 2020, 2020:5630130.

16. Cui L, Jingwen R, Minying Z, Guanheng H, Hao L: Effects of acupuncture combined with cognitive behavioral therapy on sleep quality, sleep belief and attitude in patients with chronic insomnia. *Guangdong Medical Journal* 2020, 41(10):1005-1009.

17. Ruan JW, Wang CH, Liao XX, Yan YS, Hu YH, Rao ZD, Wen M, Zeng XX, Lai XX: Electroacupuncture treatment of chronic insomniacs. *Chin Med J (Engl)* 2009, 122(23):2869-2873.



18. Yin X, Gou M, Xu J, Dong B, Yin P, Masquelin F, Wu J, Lao L, Xu S: Efficacy and safety of acupuncture treatment on primary insomnia: a randomized controlled trial. *Sleep medicine* 2017, 37:193-200.
19. Pei W, Peng R, Gu Y, Zhou X, Ruan J: Research trends of acupuncture therapy on insomnia in two decades (from 1999 to 2018):a bibliometric analysis. *BMC complementary and alternative medicine* 2019, 19(1):225.
20. Gorban AN, Makarov VA, Tyukin IY: The unreasonable effectiveness of small neural ensembles in high-dimensional brain. *Physics of life reviews* 2019, 29:55-88.
21. Bresch E, Großekathöfer U, Garcia-Molina G: Recurrent Deep Neural Networks for Real-Time Sleep Stage Classification From Single Channel EEG. *Frontiers in computational neuroscience* 2018, 12:85.
22. Hassan AR, Bhuiyan MIH: Automated identification of sleep states from EEG signals by means of ensemble empirical mode decomposition and random under sampling boosting. *Computer methods and programs in biomedicine* 2017, 140:201-210.
23. Schulz KF, Altman DG, Moher D: CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed)* 2010, 340:c332.
24. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, Moher D: Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT statement. *Journal of evidence-based medicine* 2010, 3(3):140-155.
25. Wang C, Yang WJ, Yu XT, Fu C, Li JJ, Wang J, Xu WL, Zheng YX, Chen XY, Chen YF: Acupuncture for insomnia with short sleep duration: protocol for a randomised controlled trial. *BMJ open* 2020, 10(3):e033731.
26. Battle DE: Diagnostic and Statistical Manual of Mental Disorders (DSM). *CoDAS* 2013, 25(2):191-192.

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4 27. Sateia MJ: International classification of sleep disorders-third edition: highlights and  
5 modifications. *Chest* 2014, 146(5):1387-1394.  
6  
7 28. Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD: Management of  
8 Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American  
9 College of Physicians. *Annals of internal medicine* 2016, 165(2):125-133.  
10  
11 29. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh  
12 Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry*  
13 *research* 1989, 28(2):193-213.  
14  
15 30. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A:  
16 The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and  
17 non-clinical samples: A systematic review and meta-analysis. *Sleep medicine reviews*  
18 2016, 25:52-73.  
19  
20 31. Robinson BE, Kelley L: Concurrent validity of the Beck Depression Inventory as a  
21 measure of depression. *Psychological reports* 1996, 79(3 Pt 1):929-930.  
22  
23 32. Piotrowski C: Use of the Beck Depression Inventory in clinical practice.  
24 *Psychological reports* 1996, 79(3 Pt 1):873-874.  
25  
26 33. Carney CE, Ulmer C, Edinger JD, Krystal AD, Knauss F: Assessing depression  
27 symptoms in those with insomnia: an examination of the beck depression inventory  
28 second edition (BDI-II). *Journal of psychiatric research* 2009, 43(5):576-582.  
29  
30 34. Beck AT, Epstein N, Brown G, Steer RA: An inventory for measuring clinical  
31 anxiety: psychometric properties. *Journal of consulting and clinical psychology* 1988,  
32 56(6):893-897.  
33  
34 35. Nyer M, Farabaugh A, Fehling K, Soskin D, Holt D, Papakostas GI, Pedrelli P, Fava  
35 M, Pisoni A, Vitolo O *et al*: Relationship between sleep disturbance and depression,  
36 anxiety, and functioning in college students. *Depression and anxiety* 2013,  
37 30(9):873-880.  
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4 36. Morin CM, Vallières A, Ivers H: Dysfunctional beliefs and attitudes about sleep  
5 (DBAS): validation of a brief version (DBAS-16). *Sleep* 2007, 30(11):1547-1554.  
6  
7 37. Chung KF, Ho FY, Yeung WF: Psychometric Comparison of the Full and  
8 Abbreviated Versions of the Dysfunctional Beliefs and Attitudes about Sleep Scale.  
9  
10 *Journal of clinical sleep medicine : JCSM : official publication of the American Academy*  
11 *of Sleep Medicine* 2016, 12(6):821-828.  
12  
13 38. Ramaswamy SM, Weerink MAS, Struys M, Nagaraj SB: Dexmedetomidine-induced  
14 deep sedation mimics non-rapid eye movement stage 3 sleep: large-scale validation using  
15 machine learning. *Sleep* 2021, 44(2).  
16  
17 39. Abou Jaoude M, Sun H, Pellerin KR, Pavlova M, Sarkis RA, Cash SS, Westover MB,  
18 Lam AD: Expert-level automated sleep staging of long-term scalp  
19 electroencephalography recordings using deep learning. *Sleep* 2020, 43(11).  
20  
21 40. Malhotra RK, Kirsch DB, Kristo DA, Olson EJ, Aurora RN, Carden KA, Chervin  
22 RD, Martin JL, Ramar K, Rosen CL *et al*: Polysomnography for Obstructive Sleep Apnea  
23 Should Include Arousal-Based Scoring: An American Academy of Sleep Medicine  
24 Position Statement. *Journal of clinical sleep medicine : JCSM : official publication of the*  
25 *American Academy of Sleep Medicine* 2018, 14(7):1245-1247.  
26  
27 41. Wilt TJ, MacDonald R, Brasure M, Olson CM, Carlyle M, Fuchs E, Khawaja IS,  
28 Diem S, Koffel E, Ouellette J *et al*: Pharmacologic Treatment of Insomnia Disorder: An  
29 Evidence Report for a Clinical Practice Guideline by the American College of Physicians.  
30  
31 *Annals of internal medicine* 2016, 165(2):103-112.  
32  
33 42. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, Espie  
34 CA, Garcia-Borreguero D, Gjerstad M, Gonçalves M *et al*: European guideline for the  
35 diagnosis and treatment of insomnia. *Journal of sleep research* 2017, 26(6):675-700.  
36  
37 43. Kathol RG, Arnedt JT: Cognitive Behavioral Therapy for Chronic Insomnia:  
38 Confronting the Challenges to Implementation. *Annals of internal medicine* 2016,  
39 165(2):149-150.  
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4 44. Ree M, Junge M, Cunningham D: Australasian Sleep Association position statement  
5 regarding the use of psychological/behavioral treatments in the management of insomnia  
6 in adults. *Sleep medicine* 2017, 36 Suppl 1:S43-s47.  
7  
8  
9  
10 45. Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia  
11 MJ, Troxel WM, Zhou ES, Kazmi U *et al*: Behavioral and psychological treatments for  
12 chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical  
13 practice guideline. *Journal of clinical sleep medicine : JCSM : official publication of the*  
14 *American Academy of Sleep Medicine* 2021, 17(2):255-262.  
15  
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17  
18 46. Coutaux A: Non-pharmacological treatments for pain relief: TENS and acupuncture.  
19 *Joint bone spine* 2017, 84(6):657-661.  
20  
21  
22  
23 47. Iravani S, Kazemi Motlagh AH, Emami Razavi SZ, Shahi F, Wang J, Hou L, Sun W,  
24 Afshari Fard MR, Aghili M, Karimi M *et al*: Effectiveness of Acupuncture Treatment on  
25 Chemotherapy-Induced Peripheral Neuropathy: A Pilot, Randomized, Assessor-Blinded,  
26 Controlled Trial. *Pain research & management* 2020, 2020:2504674.  
27  
28  
29  
30 48. Zhang L, Fabbri D, Upender R, Kent D: Automated sleep stage scoring of the Sleep  
31 Heart Health Study using deep neural networks. *Sleep* 2019, 42(11).  
32  
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34  
35 49. Feige B, Baumgartner B, Meyer D, Riemann D: The Relationship Between PSG and  
36 Morning/Evening Emotional Parameters in Patients With Insomnia Disorder and Good  
37 Sleepers. *Frontiers in psychology* 2018, 9:2712.  
38  
39  
40  
41 50. Lajnef T, Chaibi S, Ruby P, Aguera PE, Eichenlaub JB, Samet M, Kachouri A, Jerbi  
42 K: Learning machines and sleeping brains: Automatic sleep stage classification using  
43 decision-tree multi-class support vector machines. *Journal of neuroscience methods* 2015,  
44 250:94-105.  
45  
46  
47  
48 51. Qu W, Wang Z, Hong H, Chi Z, Feng DD, Grunstein R, Gordon C: A Residual  
49 Based Attention Model for EEG Based Sleep Staging. *IEEE journal of biomedical and*  
50 *health informatics* 2020, 24(10):2833-2843.  
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4 52. Wang Y, Loparo KA, Kelly MR, Kaplan RF: Evaluation of an automated  
5 single-channel sleep staging algorithm. *Nature and science of sleep* 2015, 7:101-111.  
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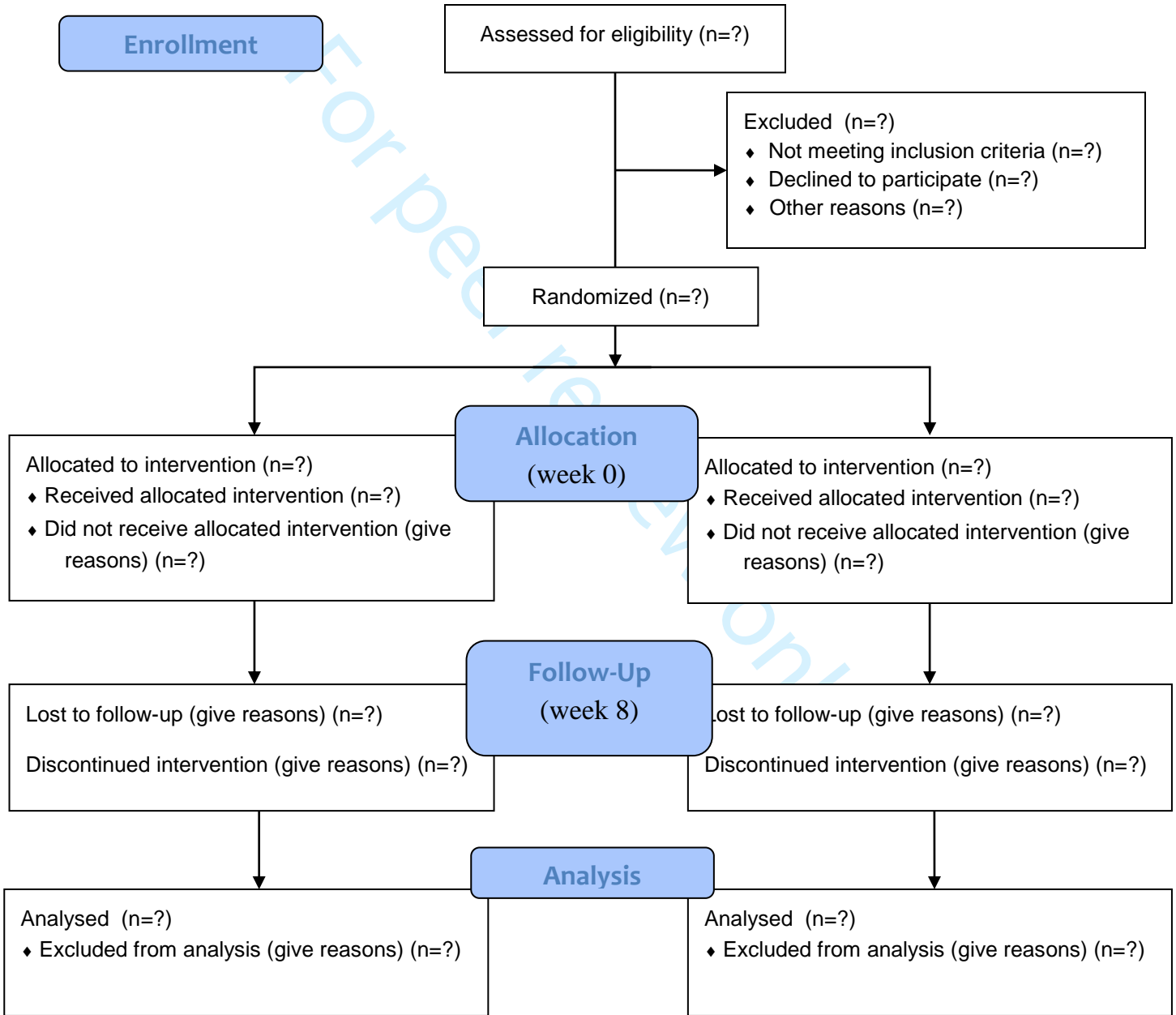
Fig 1. CONSORT 2010 Flow Diagram

Fig 2. Location of acupoints

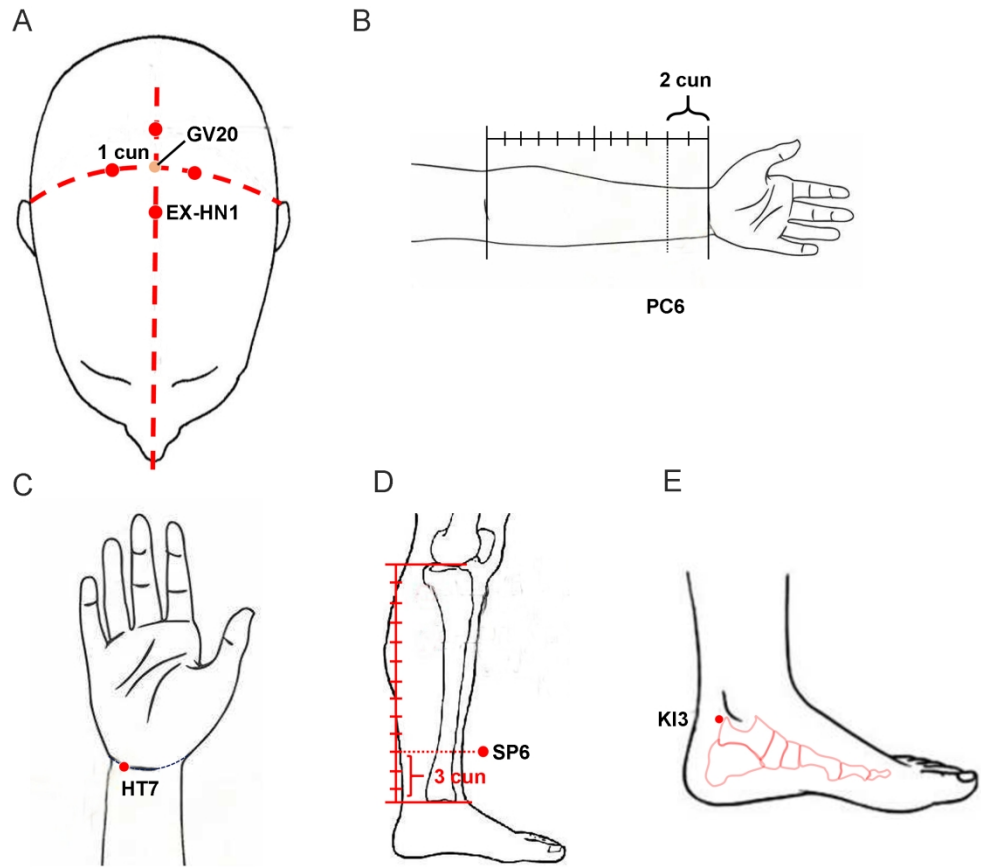
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**CONSORT 2010 Flow Diagram**



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location of accupoints

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

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | <u>1</u>                 |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | <u>1</u>                 |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | <u>1</u>                 |
| Protocol version                  | 3       | Date and version identifier  | <u>1</u>                 |
| Funding                           | 4       | Sources and types of financial, material, and other support  | <u>12</u>                |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | <u>1,12</u>              |
|                                   | 5b      | Name and contact information for the trial sponsor   | <u>12</u>                |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | <u>12</u>                |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | <u>NA</u>                |

|    |   |     |  |                           |
|----|---|-----|--|---------------------------|
| 1  | <b>Introduction</b>                                       |     |  |                           |
| 2  |   |     |  |                           |
| 3  | Background and rationale                                  | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention   | <u>3-4</u>                |
| 4  |   |     |  |                           |
| 5  |   |     |  |                           |
| 6  |   | 6b  | Explanation for choice of comparators  | <u>5</u>                  |
| 7  |   |     |  |                           |
| 8  | Objectives  | 7   | Specific objectives or hypotheses  | <u>4</u>                  |
| 9  |   |     |  |                           |
| 10 | Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  | <u>4</u>                  |
| 11 |   |     |  |                           |
| 12 |   |     |  |                           |
| 13 |   |     |  |                           |
| 14 | <b>Methods: Participants, interventions, and outcomes</b> |     |  |                           |
| 15 |   |     |  |                           |
| 16 | Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained   | <u>4-5</u>                |
| 17 |   |     |  |                           |
| 18 |   |     |  |                           |
| 19 | Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)   | <u>6</u>                  |
| 20 |   |     |  |                           |
| 21 |   |     |  |                           |
| 22 | Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered   | <u>6-7</u>                |
| 23 |   |     |  |                           |
| 24 |   |     |  |                           |
| 25 |   |     |  |                           |
| 26 |   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)   | <u>6</u>                  |
| 27 |   |     |  |                           |
| 28 |   |     |  |                           |
| 29 |   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)  | <u>6</u>                  |
| 30 |   |     |  |                           |
| 31 |   |     |  |                           |
| 32 |   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial  | <u>6</u>                  |
| 33 |   |     |  |                           |
| 34 | Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | <u>7-9</u>                |
| 35 |   |     |  |                           |
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| 39 |   |     |  |                           |
| 40 | Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)   | <u>4,Table 1,Figure 1</u> |
| 41 |   |     |  |                           |
| 42 |   |     |  |                           |
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|---|-------------|----|---|------------|
| 1 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |            |
| 2 |             |    |   |            |
| 3 |             |    |   |            |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | <u>8-9</u> |
| 5 |             |    |   |            |

**Methods: Assignment of interventions (for controlled trials)**

|    |                                  |     |  |          |
|----|----------------------------------|-----|--|----------|
| 8  | Allocation:                      |     |  | <u>5</u> |
| 9  |                                  |     |  |          |
| 10 | Sequence generation              | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | <u>5</u> |
| 11 |                                  |     |  |          |
| 12 |                                  |     |  |          |
| 13 |                                  |     |  |          |
| 14 |                                  |     |  |          |
| 15 |                                  |     |  |          |
| 16 | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  | <u>5</u> |
| 17 |                                  |     |  |          |
| 18 |                                  |     |  |          |
| 19 |                                  |     |  |          |
| 20 | Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | <u>5</u> |
| 21 |                                  |     |  |          |
| 22 |                                  |     |  |          |
| 23 |                                  |     |  |          |
| 24 | Blinding (masking)               | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | <u>5</u> |
| 25 |                                  |     |  |          |
| 26 |                                  |     |  |          |
| 27 |                                  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | <u>5</u> |
| 28 |                                  |     |  |          |
| 29 |                                  |     |  |          |
| 30 |                                  |     |  |          |

**Methods: Data collection, management, and analysis**

|    |                         |     |  |          |
|----|-------------------------|-----|--|----------|
| 31 |                         |     |  |          |
| 32 |                         |     |  |          |
| 33 | Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | <u>9</u> |
| 34 |                         |     |  |          |
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| 40 |                         | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  | <u>9</u> |
| 41 |                         |     |  |          |
| 42 |                         |     |  |          |

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|    |                                 |     |   |             |
|----|---------------------------------|-----|---|-------------|
| 1  | Data management                 | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol   | <u>9-10</u> |
| 2  |                                 |     |   |             |
| 3  |                                 |     |   |             |
| 4  |                                 |     |   |             |
| 5  | Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | <u>9-10</u> |
| 6  |                                 |     |   |             |
| 7  |                                 |     |   |             |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | <u>9-19</u> |
| 9  |                                 |     |   |             |
| 10 |                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | <u>9-10</u> |
| 11 |                                 |     |   |             |
| 12 |                                 |     |   |             |
| 13 |                                 |     |   |             |
| 14 | <b>Methods: Monitoring</b>      |     |   |             |
| 15 |                                 |     |   |             |
| 16 | Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | <u>9-10</u> |
| 17 |                                 |     |   |             |
| 18 |                                 |     |   |             |
| 19 |                                 |     |   |             |
| 20 |                                 |     |   |             |
| 21 |                                 |     |   |             |
| 22 |                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | <u>9-10</u> |
| 23 |                                 |     |   |             |
| 24 |                                 |     |   |             |
| 25 | Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | <u>9-10</u> |
| 26 |                                 |     |   |             |
| 27 |                                 |     |   |             |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | <u>9-10</u> |
| 29 |                                 |     |   |             |
| 30 |                                 |     |   |             |
| 31 |                                 |     |   |             |
| 32 | <b>Ethics and dissemination</b> |     |   |             |
| 33 |                                 |     |   |             |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | <u>5</u>    |
| 35 |                                 |     |   |             |
| 36 |                                 |     |   |             |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | <u>NA</u>   |
| 38 |                                 |     |   |             |
| 39 |                                 |     |   |             |
| 40 |                                 |     |   |             |
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|    |                               |     |  |   |
|----|-------------------------------|-----|--|---|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)   | 6                                       |
| 2  |                               |     |  |   |
| 3  |                               |     |  |   |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable  | 6                                       |
| 5  |                               |     |  |   |
| 6  |                               |     |  |   |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial   | 6                                       |
| 8  |                               |     |  |   |
| 9  |                               |     |  |   |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site  | 12                                      |
| 11 |                               |     |  |   |
| 12 |                               |     |  |   |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators  | 6                                       |
| 14 |                               |     |  |   |
| 15 |                               |     |  |   |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  | 6                                       |
| 17 |                               |     |  |   |
| 18 |                               |     |  |   |
| 19 |                               |     |  |   |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 6                                       |
| 21 |                               |     |  |   |
| 22 |                               |     |  |   |
| 23 |                               |     |  |   |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers   | 6                                       |
| 25 |                               |     |  |   |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code  | 6                                       |
| 27 |                               |     |  |   |
| 28 |                               |     |  |   |
| 29 |                               |     |  |   |
| 30 | <b>Appendices</b>             |     |  |   |
| 31 |                               |     |  |   |
| 32 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates   | <u>See The Ethics Approval Document</u> |
| 33 |                               |     |  |   |
| 34 |                               |     |  |   |
| 35 |                               |     |  |   |
| 36 |                               |     |  |   |
| 37 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable   | <u>NA</u>                               |
| 38 |                               |     |  |   |
| 39 |                               |     |  |   |

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1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
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# BMJ Open

## Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2022-063442.R2   |
| Article Type:                   | Protocol   |
| Date Submitted by the Author:   | 20-Nov-2022  |
| Complete List of Authors:       | Pei, Wenya; Sun Yat-sen University First Affiliated Hospital<br>He, Te; South China University of Technology<br>Yang, Pei; South China University of Technology<br>Lv, Xiaozhou; Sun Yat-sen University First Affiliated Hospital<br>Jiao, Boyu; Sun Yat-sen University First Affiliated Hospital<br>Meng, Fanqi; Sun Yat-sen University First Affiliated Hospital<br>Yan, Yingshuo; Sun Yat-sen University First Affiliated Hospital<br>Cui, Liqian; Sun Yat-sen University First Affiliated Hospital<br>He, Guanheng; Sun Yat-sen University First Affiliated Hospital<br>Zhou, Xin; Sun Yat-sen University First Affiliated Hospital<br>Wen, Guihua; South China University of Technology<br>Ruan, Jingwen; Sun Yat-sen University First Affiliated Hospital,<br>Lu, Liming; Guangzhou University of Chinese Medicine |
| <b>Primary Subject Heading</b>: | Complementary medicine   |
| Secondary Subject Heading:      | Health services research, Neurology, Public health   |
| Keywords:                       | CLINICAL PHYSIOLOGY, Rehabilitation medicine < INTERNAL MEDICINE, COMPLEMENTARY MEDICINE, REHABILITATION MEDICINE  |
|                                 |  |

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Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in  
patients with insomnia: study protocol for a randomized controlled trial

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## Abstract

### Introduction

Insomnia affects physical and mental health due to the lack of continuous and complete sleep architecture. Polysomnograms (PSGs) are used to record electrical information to perform sleep architecture using deep learning. Although acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) could not only improve sleep quality, solve anxiety, depression but also ameliorate poor sleep habits and detrimental cognition. Therefore, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture with deep learning.

### Methods and analysis

This randomized controlled trial will evaluate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia. Participants will be randomized to receive either electroacupuncture combined with CBT-I or sham acupuncture combined with CBT-I and followed up for four weeks. The primary outcome is sleep quality, which is evaluated by the Pittsburgh sleep quality index(PSQI). The secondary outcome measures include a measurement of depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events. Sleep architecture will be assessed using deep learning on PSGs.

### Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals. The results of this trial will be disseminated through peer-reviewed publications and conference abstracts or posters.

### Trial registration number

CTR2100052502

**Keywords:** insomnia, cognitive behavioral therapy for insomnia, electroacupuncture, randomized controlled trial

### Strengths and limitations of this study

- This study will investigate the efficacy and effectiveness of electroacupuncture combined with CBT-I.
- We will observe the effects of electroacupuncture combined with CBT-I on sleep quality and sleep beliefs and attitudes of patients with insomnia.
- We will use deep learning to observe the effects of electroacupuncture combined with CBT-I on sleep architecture in different dimensions.
- The efficacy and effectiveness of electroacupuncture on sleep quality and sleep beliefs and attitudes of patients with insomnia will be further studied in the future.

## Introduction

Insomnia is characterized by difficulties in initiating or maintaining sleep or impaired daytime functioning, which impact both physical and mental health<sup>[1-3]</sup>. The lack of continuous and complete sleep architecture due to long-term fragmented and light sleep in patients with insomnia causes a decrease in sleep quality, which affects daily functions, and even induces anxiety, depression, and other mental symptoms<sup>[4-6]</sup>. With the increasing pressures in daily life and work, insomnia is becoming a public health problem that needs to be solved urgently as it worsens the quality of life of patients, burdens caregivers, and increases social and economic costs<sup>[7-9]</sup>.

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for insomnia and may improve sleep quality and alleviate poor sleep cognition in patients with insomnia<sup>[10-12]</sup>. During the early stage of treatment, the sleep quality of patients with severe anxiety were improved slowly and the compliance of these patients were poor. Thus, as confirmed in previous studies, acupuncture combined with CBT-I could not only solve anxiety, depression, and other emotions caused by insomnia but also ameliorate poor sleep habits and detrimental cognition<sup>[13-16]</sup>.

However, there is a lack of rigorous clinical evidence on the treatment of insomnia with acupuncture combined with CBT-I; moreover, the clinical mechanism is unclear. In previous studies, we found that by analyzing polysomnograms (PSGs), electroacupuncture improves sleep architecture and prolongs the duration of slow-wave and rapid-eye-movement (REM) sleep<sup>[17-19]</sup>. But whether acupuncture combined with CBT-I improves sleep architecture requires further research.

During the past decade, the application of deep learning to automatic sleep staging using PSGs has shown promise for understanding the macrostructure of sleep. Deep learning allows the automatic extraction of features from data related to classification tasks, and the performance of deep neural networks continues to improve as the size of the dataset increases<sup>[20-22]</sup>.

Using a high-performance automatic sleep staging algorithm to analyze PSGs recordings via deep learning, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. Furthermore, this research will provide guidance for electroacupuncture combined with CBT-I using artificial intelligence.

## Methods

### Study design

The study will be an assessor-blinded, randomized controlled trial. The protocol was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). We will follow the Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines for the design and reporting of the trial<sup>[23, 24]</sup>. The flowchart of the trial is presented in Figure 1, and the schedule of enrolment, interventions, and outcome assessments are presented in Table 1.

Sample size calculations: Referring to the previous literature<sup>[25]</sup>, we assume that the expected PSQI value of the observation group is  $9.45 \pm 1.84$  and the control  $6.43 \pm 2.10$ . We determine that a sample size of 11 per group would provide a power of 90% and an alpha level of 0.05, which would allow us to detect a difference in PSQI score between the two groups. Allowing for a 20% dropout rate, a sample size of 30 in each group is sufficient to meet statistical requirements.

### Randomization, allocation, and blinding

Patients who are interested in participating in the trial will initially be screened by phone and then asked to participate in a face-to-face interview to conduct further surveys. After recruiting all participants, random numbers will be generated and assigned by a central randomization system of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. The researcher who will screen the eligible patients after baseline

Table 1 Research flow chart

| Project                              | Screening                     | Observation phase            |                            |                            | Follow-up phase            |                     |
|--------------------------------------|-------------------------------|------------------------------|----------------------------|----------------------------|----------------------------|---------------------|
|                                      | assessment 0<br>pre-treatment | Assession 1<br>pre-treatment | Assession 2<br>Week 2±1day | Assession 3<br>Week 4±2day | Assession 4<br>Week 8±2day | Unplanned follow-up |
| Medical history collection           | √                             | -                            | -                          | -                          | -                          |                     |
| Sign the informed consent form       | √                             | -                            | -                          | -                          | -                          |                     |
| Inclusion criteria                   | √                             | -                            | -                          | -                          | -                          |                     |
| Exclusion criteria                   | √                             | -                            | -                          | -                          | -                          |                     |
| Basic Information                    | √                             | -                            | -                          | -                          | -                          |                     |
| Vital signs                          | √                             | √                            | √                          | √                          | √                          | ※                   |
| Index of laboratory inspection       | ※                             | ※                            | ※                          | ※                          | ※                          |                     |
| PSG                                  | -                             | √                            | -                          | √                          | -                          |                     |
| Pittsburgh sleep quality index(PSQI) | -                             | √                            | √                          | √                          | √                          |                     |
| Beck depression inventory(BDI)       | -                             | √                            | √                          | √                          | √                          |                     |
| Beck anxiety inventory(BAI)          | -                             | √                            | √                          | √                          | √                          |                     |
| DBAS-16                              | -                             | √                            | √                          | √                          | √                          |                     |
| Adverse Events                       | -                             | ※                            | ※                          | ※                          | ※                          | ※                   |
| Medication records                   | -                             | √                            | √                          | √                          | √                          |                     |
| Terminate test evaluation            | -                             | ※                            | ※                          | ※                          | ※                          |                     |

Notes: “※”Record when necessary; PSG: Long-term scalp electroencephalogram recording; DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep Scale 16 versio

1  
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3  
4 will assign patients to either the treatment or control group. Researchers, which include  
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6 statisticians, outcome assessors, and data analysts, will all be blinded to patients' group  
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8 assignments. Although acupuncturists will be not blinded to group assignment, they will  
9  
10 not be involved in outcome assessments or data analyses. In addition, all researchers will  
11  
12 undergo training for specific procedures before the trial begins.

### 13 **Participants and recruitment**

14  
15 Patients will be recruited using hospital-based advertisements in the Department of  
16  
17 Acupuncture and Department of Neurology of the First Affiliated Hospital of Sun  
18  
19 Yat-sen University from January 2022 to December 2025.

20  
21 The inclusion criteria will be as follows: (1) meets diagnostic criteria for insomnia  
22  
23 based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition<sup>[26]</sup>  
24  
25 and the International Classification of Sleep Disorders, Third Edition<sup>[27]</sup>, (2) aged 18–65  
26  
27 years, (3) experienced insomnia for more than 1 month but less than 2 years before the  
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29 start of the trial, (4) voluntarily agrees to participate in the investigation and provides  
30  
31 written informed consent before the clinical trial starts.

32  
33 The exclusion criteria will be as follows: (1) serious cardiovascular, liver, kidney, or  
34  
35 hematopoietic system disease, (2) insomnia was caused by a nervous system disease (e.g.,  
36  
37 stroke or Parkinson's disease), (3) insomnia was caused by a mental disorder, such as  
38  
39 depression or anxiety, (4) history of sleep apnea, (5) pregnant or lactating women, (6)  
40  
41 have received or currently receiving CBT-I.

42  
43 Withdrawal criteria will be as follows: (1) patient withdrawal from the trial because  
44  
45 of personal reasons, (2) patient has an adverse reaction related to acupuncture and refuses  
46  
47 to continue treatment, (3) during the follow-up period, the patient cannot be contacted  
48  
49 because of change of address and telephone number.

### 50 **Intervention**

51  
52 The intervention will begin the day following randomization. All participants will receive  
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54 20 times treatments (five times per week for 4 weeks).  
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## Observation group

### Acupuncture treatment

Patients' skin will be disinfected with 75% alcohol, and patients will be asked to lie supine and wear eye masks for a better curative effect. Each participant will receive acupuncture treatment from the same acupuncturist who has more than 5 years of clinical experience in acupuncture therapy. The temperature of the treatment room will not be lower than 25°C.

Patients in the acupuncture group will receive electroacupuncture treatment on Sishenchong (EX-HN1), bilateral Neiguan (PC6), bilateral Taixi (KI3), bilateral Shenmen (HT7), and bilateral Sanyinjiao (SP6)<sup>[28]</sup>. Tube-guided acupuncture needles will be inserted to a depth of 17-25 mm at each acupoint (acupuncture location and method for each acupoint are provided in Table 2 and Figure 2). A low-frequency electronic pulse therapy instrument (G6805-2A, Shanghai Huayi Medical Instrument Co., Shanghai, China) will be used with 10-Hz continuous waves, and the current will range from 1 to 5 mA which will be adjusted based on the tolerance of each patient.

### CBT-I treatment

CBT-I will be given while acupuncture treatment is in progress. The intervention will consist of behavioral components (e.g. sleep restriction and stimulus control), cognitive components (e.g., cognitive restructuring and paradoxical intention), progressive muscle relaxation, and sleep hygiene<sup>[29]</sup>.

## Control group

The procedure for the control group will be the same as that for the observation group with no CBT-I treatment. The major difference in interventions between the two groups being the tube needling method, in which no needle will be inserted through the tube for patients in the control group. To mimic the sensation of a real needle being inserted into the body, the acupuncturist will place the tube close to the skin at the acupoint and tap the top of the tube.

## Quality control

The trial will be conducted under the supervision of the First Affiliated Hospital of Sun Yat-sun University. A qualified clinical trial expert will be invited to monitor the study to identify problems during the trial, examine collected data, and control bias.

## Outcome measures

### Primary outcome

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is an internationally established tool that is used to evaluate sleep quality. The scale includes seven dimensions that consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication, and daytime dysfunction. The score correlates adversely with sleep quality which a higher score means the sleep quality is worse, and each factor has a score of 0 to 3 to provide a total score of 21 points<sup>[30, 31]</sup>.

### Secondary outcomes

#### The Beck depression inventory

The Beck depression inventory (BDI) is a valid self-assessment index to measure depression severity and consists of 13 items. Each item is scored from 0 to 3 (0 to 4 indicates no depression, 5 to 7 indicates mild depression, 8 to 15 indicates moderate depression), with a score of 16 points or more considered as severe depression<sup>[32-34]</sup>.

#### The Beck anxiety inventory

The Beck anxiety inventory (BAI) is used to assess the degree of anxiety and consists of 21 items scored from 1 to 4 (15 to 25 points indicates mild anxiety, 26 to 35 points indicates moderate anxiety, and 36 points is considered severe anxiety)<sup>[35, 36]</sup>.

#### The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version (DBAS-16) is used to evaluate maladaptive cognitions associated with sleep. There are 16 items in the index, which are divided into four factors comprising consequences of insomnia, worry about



Table 2 Acupuncture location and method for each acupoint

| Acupoint             | Location   | Needling method  |
|----------------------|--|--|
| Sishenchong (EX-HN1) | On the parietal region, 1 cun anterior, posterior and lateral to Baihui, 4 acupoints totally.  | The angle between the needle tip and the scalp is 30°. Move the needle tip backward along the anteriore posterior midline, and then insert the needle 0.5 cun. |
| Neiguan(PC6)         | On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist. | Puncture perpendicularly 1-1.5 cun.  |
| Taixi (KI3)          | In the depression between the tip of the medial malleolus and the Achilles tendon.   | Puncture perpendicularly 0.5-1 cun.  |
| Shenmen (HT7)        | On the palmar ulnar end of the transverse crease of the wrist, and on the radial aspect of the tendon of the ulnar flexor m. of the wrist.             | Puncture perpendicularly 0.5-1 cun.  |
| Sanyinjiao (SP6)     | Posterior to the mesial border of the tibia, and 3 cun above the tip of the medial malleolus   | Puncture perpendicularly 1-1.5 cun.  |

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4 sleep, sleep expectations, and medication. These factors are scored on a scale of  
5 1–5 (strongly disagree to strongly agree). The total score is positively correlated with the  
6 reasonableness of sleep beliefs and attitudes<sup>[37, 38]</sup>.  
7  
8

### 9 **Sleep staging**

10 The PARADISEP&D9600 (U.S.) Polysomnography Monitoring and Analysis System  
11 will be used to simultaneously monitor EEG, EOG, and EMG. A large clinical dataset of  
12 PSG recordings will be used to train a hybrid convolutional neural network (CNN) and  
13 recurrent neural network (RNN) to learn effective and generalizable features for sleep  
14 stage scoring<sup>[39, 40]</sup>. Then clinical data will be used to identify the deep learning  
15 algorithm. Sleep staging for both datasets will be performed by expert sleep technicians  
16 in nonoverlapping 30-s epochs according to standards by the American Academy of  
17 Sleep Medicine (AASM), as one of five stages: wake (W), non-rapid eye movement (REM)  
18 stage 1 (N1), non-REM stage 2 (N2), non-REM stage 3 (N3), and rapid eye  
19 movement (REM)<sup>[41]</sup>.  
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### 31 **Adverse events**

32 During treatment and four weeks after treatment, a questionnaire will be administered to  
33 evaluate the various discomforts that may be caused by acupuncture: hangover, addiction,  
34 tolerance, fatigue after waking, insomnia rebound, daytime alertness, cognitive function,  
35 and behavior ability.  
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### 41 **Patients and public involvement**

42 Patients and the public are not involved in the design or conduct of the study or the  
43 outcome measures, and no attempt will be made to assess the burden of the intervention  
44 on the patients themselves. The results of this study will be disseminated to study  
45 participants via the website of our hospitals.  
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### 50 **Statistical analysis**

51 All analyses will be performed on the intention-to-treat population of participants who  
52 had at least one treatment. Missing data will be replaced according to the principle of the  
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4 last observation carried forward. Data analyses will be performed using the SPSS version  
5 25 (IBM Corp.) software. All available data will be analyzed descriptively. For  
6  
7 continuous data, the normality test will be applied at the beginning of the analysis.  
8  
9 Results will be presented as means, standard deviations, and 95% confidence intervals  
10  
11 (CIs) for continuous data that conform to the normal distribution and medians, quartiles,  
12  
13 and ranges for rank data and continuous data that are not normally distributed. Discrete  
14  
15 data will be presented as percentages.  
16

17 We will first examine the descriptive data for sample characteristics at baseline, and  
18  
19 independent samples t-tests will be used to compare groups for continuous variables,  
20  
21 whereas chi-square analysis will be used to compare groups for dichotomous variables.  
22  
23 Second, we will perform two series of repeated-measures and univariate analyses of  
24  
25 covariance (ANCOVA) models to examine treatment effects. We will use  
26  
27 repeated-measures ANCOVAs to analyze the primary and secondary outcome measures  
28  
29 (i.e., PSQI, BDI, BAI, DBAS-16, and sleep staging scores) from pre-treatment to  
30  
31 post-treatment. If a significant effect is observed, we will conduct posthoc paired samples  
32  
33 t-tests to examine within-group changes in study outcomes. For all study outcomes, we  
34  
35 will then perform univariate ANCOVAs to test for group differences in post-treatment  
36  
37 values while controlling for relevant covariates. This process will be repeated to examine  
38  
39 changes in study outcomes from pretreatment to postnatal follow-up.  
40

41 When necessary, ITT analysis and sensitivity analysis will be used to assess the  
42  
43 robustness of the conclusions of the entire clinical trial. To evaluate the consistency of the  
44  
45 trial and explore the factors that affect efficacy or prognosis, subgroup analysis will be  
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47 conducted to identify the population with better efficacy. Safety analysis will be used to  
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49 assess the incidence of adverse events and related symptoms in patients with insomnia  
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51 during treatment and follow-up.  
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## Limitations

Currently, CBT-I is recommended as a first-line treatment for insomnia, but it is limited in clinical practice especially in developing countries such as China<sup>[42-45]</sup>. As a complementary alternative therapy with a long history in China, acupuncture has been used as a clinical treatment for insomnia with fewer adverse effects and less permanent damage in previous studies<sup>[13, 14, 16]</sup>. In this study, we will focus on whether electroacupuncture combined with CBT-I could influence sleep quality and sleep architecture, but whether acupuncture therapy alone could influence sleep habits and correct cognition, also sleep architecture worth further research.

During the past decade, there have been various advances in automated sleep staging of PSGs data using the ability of deep learning methods to automatically extract features from data that are relevant to the classification, moreover, the performance of deep neural networks continues to improve as datasets become larger<sup>[46-50]</sup>. To analyze the effects of electroacupuncture combined with CBT-I on sleep architecture, deep learning will be used to analyze PSGs in various clinical settings in this study. But due to lack of acceptability among patients, some of the participants received placebo treatment will drop, which may make analyses no meaningful due to the small number of participants in each arm. Notwithstanding, we will be able to optimize the randomized design and statistical analysis to avoid systematic errors and minimize the bias.

## Acknowledgments

Not applicable.

## Footnotes

Contributors: Wenya Pei and Te He designed the trial protocol and drafted the manuscript. Liming Lu, Jingwen Ruan, and Guihua Wen revised the manuscript. Pei Yang, Xiaozhou Lv, and Boyu Jiao will plan the data analysis. Liqian Cui, Yingshuo Yan, Fanqi Meng,

1  
2  
3  
4 Guanheng He, and Xin Zhou will participate in participant recruitment. All authors  
5 discussed, read, and revised the manuscript, and all approved the publication of this  
6 protocol.  
7

8  
9 Funding: The study was supported by the Key R&D Program of Guangdong Province  
10 (2020B1111120001).  
11

12  
13 Competing interests: None declared.  
14

15 Patient consent for publication: Not applicable  
16

17 Provenance and peer review: Not commissioned; externally peer-reviewed.  
18  
19

## 20 21 Ethics statements

22 Patient consent for publication

23 Not applicable.  
24

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27 Ethics approval and consent to participate: The study was approved by the ethics  
28 committee of the First Affiliated Hospital of Sun Yat-sun University (2021763).  
29

30  
31 Participants will be included only after they provide written informed consent. The study  
32 was registered in the Chinese Clinical Trial Registry (No.ChiCTR2100052502,  
33 30/10/2021).  
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## 35 36 37 References

- 38 1. Riemann D, Benz F, Dressle RJ, Espie CA, Johann AF, Blanken TF, Leerssen J,  
39 Wassing R, Henry AL, Kyle SD et al: Insomnia disorder: State of the science and  
40 challenges for the future. *Journal of sleep research* 2022, 31(4):e13604.  
41
- 42 2. Chan WS, Levsen MP, McCrae CS: A meta-analysis of associations between obesity  
43 and insomnia diagnosis and symptoms. *Sleep medicine reviews* 2018, 40:170-182.  
44
- 45 3. Wickwire EM: The Value of Digital Insomnia Therapeutics: What We Know and  
46 What We Need To Know. *Journal of clinical sleep medicine : JCSM : official publication*  
47 of the American Academy of Sleep Medicine 2019, 15(1):11-13.  
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3  
4 4. Kalmbach DA, Anderson JR, Drake CL: The impact of stress on sleep: Pathogenic  
5 sleep reactivity as a vulnerability to insomnia and circadian disorders. *Journal of sleep*  
6 *research* 2018, 27(6):e12710.
- 7  
8  
9  
10 5. Shekleton JA, Flynn-Evans EE, Miller B, Epstein LJ, Kirsch D, Brogna LA, Burke  
11 LM, Bremer E, Murray JM, Gehrman P et al: Neurobehavioral performance impairment  
12 in insomnia: relationships with self-reported sleep and daytime functioning. *Sleep* 2014,  
13 37(1):107-116.
- 14  
15  
16  
17 6. Cross NE, Carrier J, Postuma RB, Gosselin N, Kakinami L, Thompson C, Chouchou  
18 F, Dang-Vu TT: Association between insomnia disorder and cognitive function in  
19 middle-aged and older adults: a cross-sectional analysis of the Canadian Longitudinal  
20 Study on Aging. *Sleep* 2019, 42(8).
- 21  
22  
23  
24 7. Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML,  
25 Bixler EO: Risk factors for incident chronic insomnia: a general population prospective  
26 study. *Sleep medicine* 2012, 13(4):346-353.
- 27  
28  
29  
30 8. Zhang Y, Ren R, Lei F, Zhou J, Zhang J, Wing YK, Sanford LD, Tang X:  
31 Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia  
32 symptoms with obstructive sleep apnea: A systematic review and meta-analysis. *Sleep*  
33 *medicine reviews* 2019, 45:1-17.
- 34  
35  
36  
37 9. Kessler RC, Berglund PA, Coulouvrat C, Fitzgerald T, Hajak G, Roth T, Shahly V,  
38 Shillington AC, Stephenson JJ, Walsh JK: Insomnia, comorbidity, and risk of injury  
39 among insured Americans: results from the America Insomnia Survey. *Sleep* 2012,  
40 35(6):825-834.
- 41  
42  
43  
44 10. Kalmbach DA, Cheng P, Arnedt JT, Cuamatzi-Castelan A, Atkinson RL,  
45 Fellman-Couture C, Roehrs T, Drake CL: Improving Daytime Functioning, Work  
46 Performance, and Quality of Life in Postmenopausal Women With Insomnia: Comparing  
47 Cognitive Behavioral Therapy for Insomnia, Sleep Restriction Therapy, and Sleep  
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4 Hygiene Education. *Journal of clinical sleep medicine : JCSM : official publication of the*  
5  
6 *American Academy of Sleep Medicine* 2019, 15(7):999-1010.

7  
8 11. Espie CA, Emsley R, Kyle SD, Gordon C, Drake CL, Siriwardena AN, Cape J, Ong  
9  
10 JC, Sheaves B, Foster R et al: Effect of Digital Cognitive Behavioral Therapy for  
11  
12 Insomnia on Health, Psychological Well-being, and Sleep-Related Quality of Life: A  
13  
14 Randomized Clinical Trial. *JAMA psychiatry* 2019, 76(1):21-30.

15  
16 12. Thakral M, Von Korff M, McCurry SM, Morin CM, Vitiello MV: Changes in  
17  
18 dysfunctional beliefs about sleep after cognitive behavioral therapy for insomnia: A  
19  
20 systematic literature review and meta-analysis. *Sleep medicine reviews* 2020, 49:101230.

21  
22 13. Garland SN, Xie SX, DuHamel K, Bao T, Li Q, Barg FK, Song S, Kantoff P,  
23  
24 Gehrman P, Mao JJ: Acupuncture Versus Cognitive Behavioral Therapy for Insomnia in  
25  
26 Cancer Survivors: A Randomized Clinical Trial. *Journal of the National Cancer Institute*  
27  
28 2019, 111(12):1323-1331.

29  
30 14. Liou KT, Root JC, Garland SN, Green J, Li Y, Li QS, Kantoff PW, Ahles TA, Mao  
31  
32 JJ: Effects of acupuncture versus cognitive behavioral therapy on cognitive function in  
33  
34 cancer survivors with insomnia: A secondary analysis of a randomized clinical trial.  
35  
36 *Cancer* 2020, 126(13):3042-3052.

37  
38 15. Xing J, Wu X, Liu H, Wang J, Jiang S, Lozada A, Wang Y: Effects of  
39  
40 Electroacupuncture Therapy and Cognitive Behavioral Therapy in Chronic Insomnia: A  
41  
42 Randomized Controlled Study. *Evidence-based complementary and alternative medicine :*  
43  
44 *eCAM* 2020, 2020:5630130.

45  
46 16. Cui L, Jingwen R, Minying Z, Guanheng H, Hao L: Effects of acupuncture combined  
47  
48 with cognitive behavioral therapy on sleep quality, sleep belief and attitude in patients  
49  
50 with chronic insomnia. *Guangdong Medical Journal* 2020, 41(10):1005-1009.

51  
52 17. Ruan JW, Wang CH, Liao XX, Yan YS, Hu YH, Rao ZD, Wen M, Zeng XX, Lai  
53  
54 XX: Electroacupuncture treatment of chronic insomniacs. *Chin Med J (Engl)* 2009,  
55  
56 122(23):2869-2873.



- 1  
2  
3  
4 18. Yin X, Gou M, Xu J, Dong B, Yin P, Masquelin F, Wu J, Lao L, Xu S: Efficacy and  
5 safety of acupuncture treatment on primary insomnia: a randomized controlled trial.  
6 *Sleep medicine* 2017, 37:193-200.  
7  
8  
9 19. Pei W, Peng R, Gu Y, Zhou X, Ruan J: Research trends of acupuncture therapy on  
10 insomnia in two decades (from 1999 to 2018):a bibliometric analysis. *BMC*  
11 *complementary and alternative medicine* 2019, 19(1):225.  
12  
13 20. Gorban AN, Makarov VA, Tyukin IY: The unreasonable effectiveness of small  
14 neural ensembles in high-dimensional brain. *Physics of life reviews* 2019, 29:55-88.  
15  
16 21. Bresch E, Großekathöfer U, Garcia-Molina G: Recurrent Deep Neural Networks for  
17 Real-Time Sleep Stage Classification From Single Channel EEG. *Frontiers in*  
18 *computational neuroscience* 2018, 12:85.  
19  
20 22. Hassan AR, Bhuiyan MIH: Automated identification of sleep states from EEG  
21 signals by means of ensemble empirical mode decomposition and random under sampling  
22 boosting. *Computer methods and programs in biomedicine* 2017, 140:201-210.  
23  
24 23. Schulz KF, Altman DG, Moher D: CONSORT 2010 statement: updated guidelines  
25 for reporting parallel group randomised trials. *BMJ (Clinical research ed)* 2010,  
26 340:c332.  
27  
28 24. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A,  
29 Moher D: Revised STandards for Reporting Interventions in Clinical Trials of  
30 Acupuncture (STRICTA): Extending the CONSORT statement. *Journal of*  
31 *evidence-based medicine* 2010, 3(3):140-155.  
32  
33 25. Wang C, Yang WJ, Yu XT, Fu C, Li JJ, Wang J, Xu WL, Zheng YX, Chen XY,  
34 Chen YF: Acupuncture for insomnia with short sleep duration: protocol for a randomised  
35 controlled trial. *BMJ open* 2020, 10(3):e033731.  
36  
37 26. Battle DE: Diagnostic and Statistical Manual of Mental Disorders (DSM). *CoDAS*  
38 2013, 25(2):191-192.  
39  
40  
41  
42  
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4 27. Sateia MJ: International classification of sleep disorders-third edition: highlights and  
5 modifications. *Chest* 2014, 146(5):1387-1394.  
6  
7 28. Cui, L, Ruan, J, Zheng, M, He, G, Li H: Effects of acupuncture combined  
8 with cognitive behavioral therapy on sleep quality, sleep belief and attitude in patients  
9 with chronic insomnia. *Guangdong Medical Journal* 2020, 41(10):1005-1009.  
10  
11 29. Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD: Management of  
12 Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American  
13 College of Physicians. *Annals of internal medicine* 2016, 165(2):125-133.  
14  
15 30. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh  
16 Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry*  
17 *research* 1989, 28(2):193-213.  
18  
19 31. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A:  
20 The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and  
21 non-clinical samples: A systematic review and meta-analysis. *Sleep medicine reviews*  
22 2016, 25:52-73.  
23  
24 32. Robinson BE, Kelley L: Concurrent validity of the Beck Depression Inventory as a  
25 measure of depression. *Psychological reports* 1996, 79(3 Pt 1):929-930.  
26  
27 33. Piotrowski C: Use of the Beck Depression Inventory in clinical practice.  
28 *Psychological reports* 1996, 79(3 Pt 1):873-874.  
29  
30 34. Carney CE, Ulmer C, Edinger JD, Krystal AD, Knauss F: Assessing depression  
31 symptoms in those with insomnia: an examination of the beck depression inventory  
32 second edition (BDI-II). *Journal of psychiatric research* 2009, 43(5):576-582.  
33  
34 35. Beck AT, Epstein N, Brown G, Steer RA: An inventory for measuring clinical  
35 anxiety: psychometric properties. *Journal of consulting and clinical psychology* 1988,  
36 56(6):893-897.  
37  
38 36. Nyer M, Farabaugh A, Fehling K, Soskin D, Holt D, Papakostas GI, Pedrelli P, Fava  
39 M, Pisoni A, Vitolo O et al: Relationship between sleep disturbance and depression,  
40  
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4 anxiety, and functioning in college students. *Depression and anxiety* 2013,  
5 30(9):873-880.  
6  
7 37. Morin CM, Vallières A, Ivers H: Dysfunctional beliefs and attitudes about sleep  
8 (DBAS): validation of a brief version (DBAS-16). *Sleep* 2007, 30(11):1547-1554.  
9  
10 38. Chung KF, Ho FY, Yeung WF: Psychometric Comparison of the Full and  
11 Abbreviated Versions of the Dysfunctional Beliefs and Attitudes about Sleep Scale.  
12 *Journal of clinical sleep medicine : JCSM : official publication of the American Academy*  
13 *of Sleep Medicine* 2016, 12(6):821-828.  
14  
15 39. Ramaswamy SM, Weerink MAS, Struys M, Nagaraj SB: Dexmedetomidine-induced  
16 deep sedation mimics non-rapid eye movement stage 3 sleep: large-scale validation using  
17 machine learning. *Sleep* 2021, 44(2).  
18  
19 40. Abou Jaoude M, Sun H, Pellerin KR, Pavlova M, Sarkis RA, Cash SS, Westover MB,  
20 Lam AD: Expert-level automated sleep staging of long-term scalp  
21 electroencephalography recordings using deep learning. *Sleep* 2020, 43(11).  
22  
23 41. Malhotra RK, Kirsch DB, Kristo DA, Olson EJ, Aurora RN, Carden KA, Chervin  
24 RD, Martin JL, Ramar K, Rosen CL et al: Polysomnography for Obstructive Sleep Apnea  
25 Should Include Arousal-Based Scoring: An American Academy of Sleep Medicine  
26 Position Statement. *Journal of clinical sleep medicine : JCSM : official publication of the*  
27 *American Academy of Sleep Medicine* 2018, 14(7):1245-1247.  
28  
29 42. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groseelj L, Ellis JG, Espie  
30 CA, Garcia-Borreguero D, Gjerstad M, Gonçalves M et al: European guideline for the  
31 diagnosis and treatment of insomnia. *Journal of sleep research* 2017, 26(6):675-700.  
32  
33 43. Kathol RG, Arnedt JT: Cognitive Behavioral Therapy for Chronic Insomnia:  
34 Confronting the Challenges to Implementation. *Annals of internal medicine* 2016,  
35 165(2):149-150.  
36  
37  
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39  
40  
41  
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3  
4 44. Ree M, Junge M, Cunnington D: Australasian Sleep Association position statement  
5 regarding the use of psychological/behavioral treatments in the management of insomnia  
6 in adults. *Sleep medicine* 2017, 36 Suppl 1:S43-s47.  
7  
8  
9 45. Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia  
10 MJ, Troxel WM, Zhou ES, Kazmi U et al: Behavioral and psychological treatments for  
11 chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical  
12 practice guideline. *Journal of clinical sleep medicine : JCSM : official publication of the*  
13 *American Academy of Sleep Medicine* 2021, 17(2):255-262.  
14  
15  
16 46. Zhang L, Fabbri D, Upender R, Kent D: Automated sleep stage scoring of the Sleep  
17 Heart Health Study using deep neural networks. *Sleep* 2019, 42(11).  
18  
19  
20 47. Feige B, Baumgartner B, Meyer D, Riemann D: The Relationship Between PSG and  
21 Morning/Evening Emotional Parameters in Patients With Insomnia Disorder and Good  
22 Sleepers. *Frontiers in psychology* 2018, 9:2712.  
23  
24  
25 48. Lajnef T, Chaibi S, Ruby P, Aguera PE, Eichenlaub JB, Samet M, Kachouri A, Jerbi  
26 K: Learning machines and sleeping brains: Automatic sleep stage classification using  
27 decision-tree multi-class support vector machines. *Journal of neuroscience methods* 2015,  
28 250:94-105.  
29  
30  
31 49. Qu W, Wang Z, Hong H, Chi Z, Feng DD, Grunstein R, Gordon C: A Residual  
32 Based Attention Model for EEG Based Sleep Staging. *IEEE journal of biomedical and*  
33 *health informatics* 2020, 24(10):2833-2843.  
34  
35  
36 50. Wang Y, Loparo KA, Kelly MR, Kaplan RF: Evaluation of an automated  
37 single-channel sleep staging algorithm. *Nature and science of sleep* 2015, 7:101-111.  
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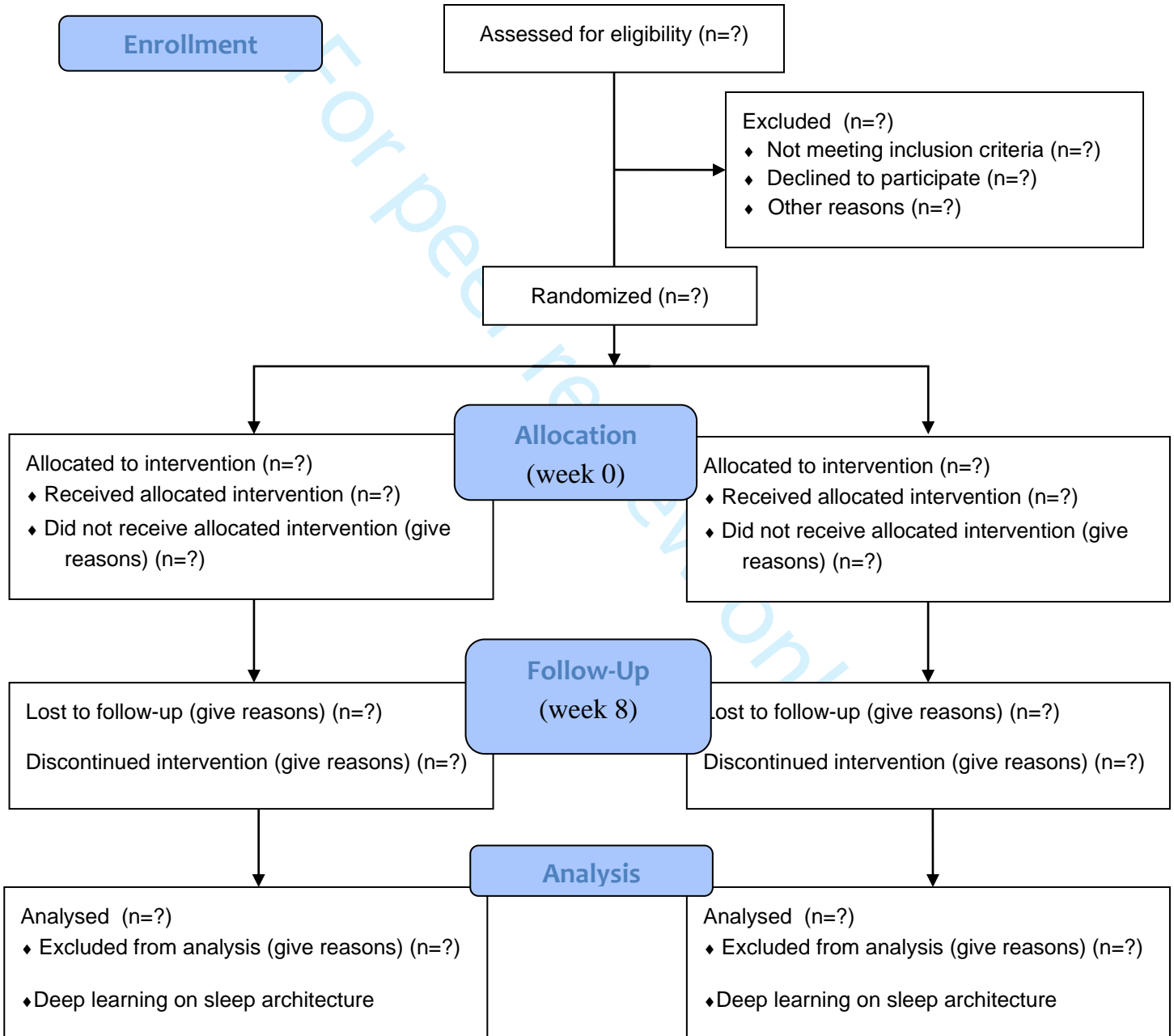
Fig 1. CONSORT 2010 Flow Diagram

Fig 2. Location of acupoints

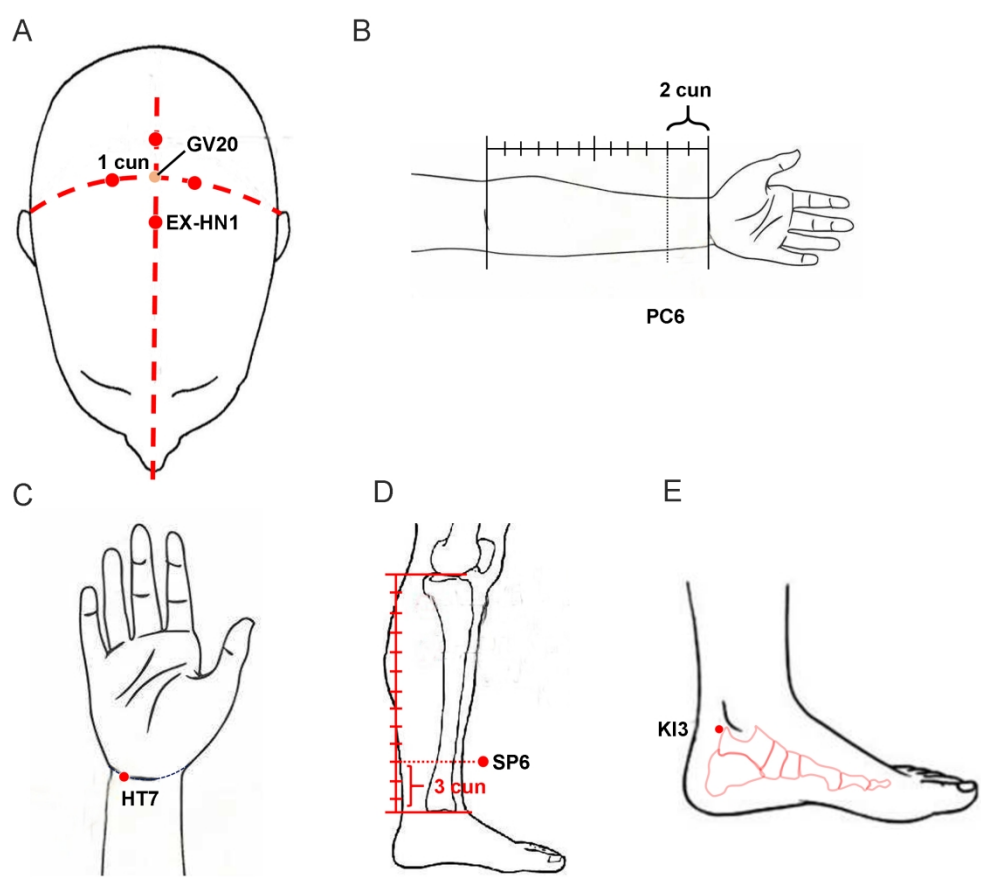
For peer review only



**CONSORT 2010 Flow Diagram**



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location of accupoints

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

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | <u>1</u>                 |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | <u>1</u>                 |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | <u>1</u>                 |
| Protocol version                  | 3       | Date and version identifier  | <u>1</u>                 |
| Funding                           | 4       | Sources and types of financial, material, and other support  | <u>12</u>                |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | <u>1,12</u>              |
|                                   | 5b      | Name and contact information for the trial sponsor   | <u>12</u>                |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | <u>12</u>                |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | <u>NA</u>                |

|    |   |     |  |                           |
|----|---|-----|--|---------------------------|
| 1  | <b>Introduction</b>                                       |     |  |                           |
| 2  |   |     |  |                           |
| 3  | Background and rationale                                  | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention   | <u>3-4</u>                |
| 4  |   |     |  |                           |
| 5  |   |     |  |                           |
| 6  |   | 6b  | Explanation for choice of comparators  | <u>5</u>                  |
| 7  |   |     |  |                           |
| 8  | Objectives  | 7   | Specific objectives or hypotheses  | <u>4</u>                  |
| 9  |   |     |  |                           |
| 10 | Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  | <u>4</u>                  |
| 11 |   |     |  |                           |
| 12 |   |     |  |                           |
| 13 |   |     |  |                           |
| 14 | <b>Methods: Participants, interventions, and outcomes</b> |     |  |                           |
| 15 |   |     |  |                           |
| 16 | Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained   | <u>4-5</u>                |
| 17 |   |     |  |                           |
| 18 |   |     |  |                           |
| 19 | Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)   | <u>6</u>                  |
| 20 |   |     |  |                           |
| 21 |   |     |  |                           |
| 22 | Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered   | <u>6-7</u>                |
| 23 |   |     |  |                           |
| 24 |   |     |  |                           |
| 25 |   |     |  |                           |
| 26 |   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)   | <u>6</u>                  |
| 27 |   |     |  |                           |
| 28 |   |     |  |                           |
| 29 |   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)  | <u>6</u>                  |
| 30 |   |     |  |                           |
| 31 |   |     |  |                           |
| 32 |   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial  | <u>6</u>                  |
| 33 |   |     |  |                           |
| 34 | Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | <u>7-9</u>                |
| 35 |   |     |  |                           |
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| 38 |   |     |  |                           |
| 39 |   |     |  |                           |
| 40 | Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)   | <u>4,Table 1,Figure 1</u> |
| 41 |   |     |  |                           |
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|----|---|-----|--|------------|
| 1  | Sample size   | 14  | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations  |            |
| 2  |   |     |  |            |
| 3  |   |     |  |            |
| 4  | Recruitment   | 15  | Strategies for achieving adequate participant enrolment to reach target sample size  | <u>8-9</u> |
| 5  |   |     |  |            |
| 6  | <b>Methods: Assignment of interventions (for controlled trials)</b> |     |  |            |
| 7  |   |     |  |            |
| 8  | Allocation:   |     |  | <u>5</u>   |
| 9  |   |     |  |            |
| 10 | Sequence  | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions   | <u>5</u>   |
| 11 | generation  |     |  |            |
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| 16 | Allocation  | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  | <u>5</u>   |
| 17 | concealment   |     |  |            |
| 18 | mechanism   |     |  |            |
| 19 |   |     |  |            |
| 20 | Implementation  | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | <u>5</u>   |
| 21 |   |     |  |            |
| 22 |   |     |  |            |
| 23 |   |     |  |            |
| 24 | Blinding (masking)  | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | <u>5</u>   |
| 25 |   |     |  |            |
| 26 |   |     |  |            |
| 27 |   | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | <u>5</u>   |
| 28 |   |     |  |            |
| 29 |   |     |  |            |
| 30 |   |     |  |            |
| 31 | <b>Methods: Data collection, management, and analysis</b>           |     |  |            |
| 32 |   |     |  |            |
| 33 | Data collection   | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | <u>9</u>   |
| 34 | methods   |     |  |            |
| 35 |   |     |  |            |
| 36 |   |     |  |            |
| 37 |   |     |  |            |
| 38 |   |     |  |            |
| 39 |   |     |  |            |
| 40 |   | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  | <u>9</u>   |
| 41 |   |     |  |            |
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| 46 |   |     |  |            |

|    |                                 |     |   |             |
|----|---------------------------------|-----|---|-------------|
| 1  | Data management                 | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol   | <u>9-10</u> |
| 2  |                                 |     |   |             |
| 3  |                                 |     |   |             |
| 4  |                                 |     |   |             |
| 5  | Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | <u>9-10</u> |
| 6  |                                 |     |   |             |
| 7  |                                 |     |   |             |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | <u>9-19</u> |
| 9  |                                 |     |   |             |
| 10 |                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | <u>9-10</u> |
| 11 |                                 |     |   |             |
| 12 |                                 |     |   |             |
| 13 |                                 |     |   |             |
| 14 | <b>Methods: Monitoring</b>      |     |   |             |
| 15 |                                 |     |   |             |
| 16 | Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | <u>9-10</u> |
| 17 |                                 |     |   |             |
| 18 |                                 |     |   |             |
| 19 |                                 |     |   |             |
| 20 |                                 |     |   |             |
| 21 |                                 |     |   |             |
| 22 |                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | <u>9-10</u> |
| 23 |                                 |     |   |             |
| 24 |                                 |     |   |             |
| 25 | Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | <u>9-10</u> |
| 26 |                                 |     |   |             |
| 27 |                                 |     |   |             |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | <u>9-10</u> |
| 29 |                                 |     |   |             |
| 30 |                                 |     |   |             |
| 31 |                                 |     |   |             |
| 32 | <b>Ethics and dissemination</b> |     |   |             |
| 33 |                                 |     |   |             |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | <u>5</u>    |
| 35 |                                 |     |   |             |
| 36 |                                 |     |   |             |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | <u>NA</u>   |
| 38 |                                 |     |   |             |
| 39 |                                 |     |   |             |
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|----|-------------------------------|-----|--|---|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)   | 6                                       |
| 2  |                               |     |  |   |
| 3  |                               |     |  |   |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable  | 6                                       |
| 5  |                               |     |  |   |
| 6  |                               |     |  |   |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial   | 6                                       |
| 8  |                               |     |  |   |
| 9  |                               |     |  |   |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site  | 12                                      |
| 11 |                               |     |  |   |
| 12 |                               |     |  |   |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators  | 6                                       |
| 14 |                               |     |  |   |
| 15 |                               |     |  |   |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  | 6                                       |
| 17 |                               |     |  |   |
| 18 |                               |     |  |   |
| 19 |                               |     |  |   |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 6                                       |
| 21 |                               |     |  |   |
| 22 |                               |     |  |   |
| 23 |                               |     |  |   |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers   | 6                                       |
| 25 |                               |     |  |   |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code  | 6                                       |
| 27 |                               |     |  |   |
| 28 |                               |     |  |   |
| 29 |                               |     |  |   |
| 30 | <b>Appendices</b>             |     |  |   |
| 31 |                               |     |  |   |
| 32 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates   | <u>See The Ethics Approval Document</u> |
| 33 |                               |     |  |   |
| 34 |                               |     |  |   |
| 35 |                               |     |  |   |
| 36 |                               |     |  |   |
| 37 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable   | <u>NA</u>                               |
| 38 |                               |     |  |   |
| 39 |                               |     |  |   |

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\*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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# BMJ Open

## Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in patients with insomnia: study protocol for a randomized controlled trial

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2022-063442.R3   |
| Article Type:                   | Protocol   |
| Date Submitted by the Author:   | 08-Dec-2022  |
| Complete List of Authors:       | Pei, Wenya; Sun Yat-sen University First Affiliated Hospital<br>He, Te; South China University of Technology<br>Yang, Pei; South China University of Technology<br>Lv, Xiaozhou; Sun Yat-sen University First Affiliated Hospital<br>Jiao, Boyu; Sun Yat-sen University First Affiliated Hospital<br>Meng, Fanqi; Sun Yat-sen University First Affiliated Hospital<br>Yan, Yingshuo; Sun Yat-sen University First Affiliated Hospital<br>Cui, Liqian; Sun Yat-sen University First Affiliated Hospital<br>He, Guanheng; Sun Yat-sen University First Affiliated Hospital<br>Zhou, Xin; Sun Yat-sen University First Affiliated Hospital<br>Wen, Guihua; South China University of Technology<br>Ruan, Jingwen; Sun Yat-sen University First Affiliated Hospital,<br>Lu, Liming; Guangzhou University of Chinese Medicine |
| <b>Primary Subject Heading</b>: | Complementary medicine   |
| Secondary Subject Heading:      | Health services research, Neurology, Public health   |
| Keywords:                       | CLINICAL PHYSIOLOGY, Rehabilitation medicine < INTERNAL MEDICINE, COMPLEMENTARY MEDICINE, REHABILITATION MEDICINE  |
|                                 |  |

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Acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) in  
patients with insomnia: study protocol for a randomized controlled trial

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Guanheng He<sup>1</sup>, Xin Zhou<sup>1</sup>, Guihua Wen<sup>2</sup>, Jingwen Ruan<sup>1</sup>, Liming Lu<sup>6</sup>

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## Abstract

### Introduction

Insomnia affects physical and mental health due to the lack of continuous and complete sleep architecture. Polysomnograms (PSGs) are used to record electrical information to perform sleep architecture using deep learning. Although acupuncture combined with cognitive-behavioral therapy for insomnia (CBT-I) could not only improve sleep quality, solve anxiety, depression but also ameliorate poor sleep habits and detrimental cognition. Therefore, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture with deep learning.

### Methods and analysis

This randomized controlled trial will evaluate the efficacy and effectiveness of electroacupuncture combined with CBT-I in patients with insomnia. Participants will be randomized to receive either electroacupuncture combined with CBT-I or sham acupuncture combined with CBT-I and followed up for four weeks. The primary outcome is sleep quality, which is evaluated by the Pittsburgh sleep quality index(PSQI). The secondary outcome measures include a measurement of depression severity, anxiety, maladaptive cognitions associated with sleep, and adverse events. Sleep architecture will be assessed using deep learning on PSGs.

### Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals. The results of this trial will be disseminated through peer-reviewed publications and conference abstracts or posters.

### Trial registration number

CTR2100052502

**Keywords:** insomnia, cognitive behavioral therapy for insomnia, electroacupuncture, randomized controlled trial

#### Strengths and limitations of this study

- This study will investigate the efficacy and effectiveness of electroacupuncture combined with CBT-I.
- We will use deep learning to observe the effects of electroacupuncture combined with CBT-I on sleep architecture in different dimensions.
- The efficacy and effectiveness of electroacupuncture on sleep quality and sleep beliefs and attitudes of patients with insomnia will be further studied in the future.
- Although we explained the randomized design and statistical analysis through ITT analysis and sensitivity analysis to some extent, systematic errors and bias remained uncertain.



## Introduction

Insomnia is characterized by difficulties in initiating or maintaining sleep or impaired daytime functioning, which impact both physical and mental health<sup>[1-3]</sup>. The lack of continuous and complete sleep architecture due to long-term fragmented and light sleep in patients with insomnia causes a decrease in sleep quality, which affects daily functions, and even induces anxiety, depression, and other mental symptoms<sup>[4-6]</sup>. With the increasing pressures in daily life and work, insomnia is becoming a public health problem that needs to be solved urgently as it worsens the quality of life of patients, burdens caregivers, and increases social and economic costs<sup>[7-9]</sup>.

Cognitive-behavioral therapy for insomnia (CBT-I) is recommended as first-line treatment for insomnia and may improve sleep quality and alleviate poor sleep cognition in patients with insomnia<sup>[10-12]</sup>. During the early stage of treatment, the sleep quality of patients with severe anxiety were improved slowly and the compliance of these patients were poor. Thus, as confirmed in previous studies, acupuncture combined with CBT-I could not only solve anxiety, depression, and other emotions caused by insomnia but also ameliorate poor sleep habits and detrimental cognition<sup>[13-16]</sup>.

However, there is a lack of rigorous clinical evidence on the treatment of insomnia with acupuncture combined with CBT-I; moreover, the clinical mechanism is unclear. In previous studies, we found that by analyzing polysomnograms (PSGs), electroacupuncture improves sleep architecture and prolongs the duration of slow-wave and rapid-eye-movement (REM) sleep<sup>[17-19]</sup>. But whether acupuncture combined with CBT-I improves sleep architecture requires further research.

During the past decade, the application of deep learning to automatic sleep staging using PSGs has shown promise for understanding the macrostructure of sleep. Deep learning allows the automatic extraction of features from data related to classification tasks, and the performance of deep neural networks continues to improve as the size of the dataset increases<sup>[20-22]</sup>.

Using a high-performance automatic sleep staging algorithm to analyze PSGs recordings via deep learning, this study will focus on the effects of electroacupuncture combined with CBT-I on sleep architecture, sleep quality, and sleep attitudes and beliefs in patients with insomnia. Furthermore, this research will provide guidance for electroacupuncture combined with CBT-I using artificial intelligence.

## Methods

### Study design

The study will be an assessor-blinded, randomized controlled trial. The protocol was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763). We will follow the Consolidated Standards of Reporting Trials and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines for the design and reporting of the trial<sup>[23, 24]</sup>. The flowchart of the trial is presented in Figure 1, and the schedule of enrolment, interventions, and outcome assessments are presented in Table 1.

Sample size calculations: Referring to the previous literature<sup>[25]</sup>, we assume that the expected PSQI value of the observation group is  $9.45 \pm 1.84$  and the control  $6.43 \pm 2.10$ . We determine that a sample size of 11 per group would provide a power of 90% and an alpha level of 0.05, which would allow us to detect a difference in PSQI score between the two groups. Allowing for a 20% dropout rate, a sample size of 30 in each group is sufficient to meet statistical requirements.

### Randomization, allocation, and blinding

Patients who are interested in participating in the trial will initially be screened by phone and then asked to participate in a face-to-face interview to conduct further surveys. After recruiting all participants, random numbers will be generated and assigned by a central randomization system of the Clinical Research and Data Center of Guangzhou University of Chinese Medicine. The researcher who will screen the eligible patients after baseline

Table 1 Research flow chart

| Project                              | Screening                     | Observation phase            |                            |                            | Follow-up phase            |                     |
|--------------------------------------|-------------------------------|------------------------------|----------------------------|----------------------------|----------------------------|---------------------|
|                                      | assessment 0<br>pre-treatment | Assession 1<br>pre-treatment | Assession 2<br>Week 2±1day | Assession 3<br>Week 4±2day | Assession 4<br>Week 8±2day | Unplanned follow-up |
| Medical history collection           | √                             | -                            | -                          | -                          | -                          |                     |
| Sign the informed consent form       | √                             | -                            | -                          | -                          | -                          |                     |
| Inclusion criteria                   | √                             | -                            | -                          | -                          | -                          |                     |
| Exclusion criteria                   | √                             | -                            | -                          | -                          | -                          |                     |
| Basic Information                    | √                             | -                            | -                          | -                          | -                          |                     |
| Vital signs                          | √                             | √                            | √                          | √                          | √                          | ※                   |
| Index of laboratory inspection       | ※                             | ※                            | ※                          | ※                          | ※                          |                     |
| PSG                                  | -                             | √                            | -                          | √                          | -                          |                     |
| Pittsburgh sleep quality index(PSQI) | -                             | √                            | √                          | √                          | √                          |                     |
| Beck depression inventory(BDI)       | -                             | √                            | √                          | √                          | √                          |                     |
| Beck anxiety inventory(BAI)          | -                             | √                            | √                          | √                          | √                          |                     |
| DBAS-16                              | -                             | √                            | √                          | √                          | √                          |                     |
| Adverse Events                       | -                             | ※                            | ※                          | ※                          | ※                          | ※                   |
| Medication records                   | -                             | √                            | √                          | √                          | √                          |                     |
| Terminate test evaluation            | -                             | ※                            | ※                          | ※                          | ※                          |                     |

Notes: “※”Record when necessary; PSG: Long-term scalp electroencephalogram recording; DBAS-16: Dysfunctional Beliefs and Attitudes about Sleep Scale 16 versio

1  
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3  
4 will assign patients to either the treatment or control group. Researchers, which include  
5  
6 statisticians, outcome assessors, and data analysts, will all be blinded to patients' group  
7  
8 assignments. Although acupuncturists will be not blinded to group assignment, they will  
9  
10 not be involved in outcome assessments or data analyses. In addition, all researchers will  
11  
12 undergo training for specific procedures before the trial begins.

### 13 **Participants and recruitment**

14  
15 Patients will be recruited using hospital-based advertisements in the Department of  
16  
17 Acupuncture and Department of Neurology of the First Affiliated Hospital of Sun  
18  
19 Yat-sen University from January 2022 to December 2025.

20  
21 The inclusion criteria will be as follows: (1) meets diagnostic criteria for insomnia  
22  
23 based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition<sup>[26]</sup>  
24  
25 and the International Classification of Sleep Disorders, Third Edition<sup>[27]</sup>, (2) aged 18–65  
26  
27 years, (3) experienced insomnia for more than 1 month but less than 2 years before the  
28  
29 start of the trial, (4) voluntarily agrees to participate in the investigation and provides  
30  
31 written informed consent before the clinical trial starts.

32  
33 The exclusion criteria will be as follows: (1) serious cardiovascular, liver, kidney, or  
34  
35 hematopoietic system disease, (2) insomnia was caused by a nervous system disease (e.g.,  
36  
37 stroke or Parkinson's disease), (3) insomnia was caused by a mental disorder, such as  
38  
39 depression or anxiety, (4) history of sleep apnea, (5) pregnant or lactating women, (6)  
40  
41 have received or currently receiving CBT-I.

42  
43 Withdrawal criteria will be as follows: (1) patient withdrawal from the trial because  
44  
45 of personal reasons, (2) patient has an adverse reaction related to acupuncture and refuses  
46  
47 to continue treatment, (3) during the follow-up period, the patient cannot be contacted  
48  
49 because of change of address and telephone number.

### 50 **Intervention**

51  
52 The intervention will begin the day following randomization. All participants will receive  
53  
54 20 times treatments (five times per week for 4 weeks).  
55  
56  
57  
58  
59  
60

## Observation group

### Acupuncture treatment

Patients' skin will be disinfected with 75% alcohol, and patients will be asked to lie supine and wear eye masks for a better curative effect. Each participant will receive acupuncture treatment from the same acupuncturist who has more than 5 years of clinical experience in acupuncture therapy. The temperature of the treatment room will not be lower than 25°C.

Patients in the acupuncture group will receive electroacupuncture treatment on Sishenchong (EX-HN1), bilateral Neiguan (PC6), bilateral Taixi (KI3), bilateral Shenmen (HT7), and bilateral Sanyinjiao (SP6)<sup>[28]</sup>. Tube-guided acupuncture needles will be inserted to a depth of 17-25 mm at each acupoint (acupuncture location and method for each acupoint are provided in Table 2 and Figure 2). A low-frequency electronic pulse therapy instrument (G6805-2A, Shanghai Huayi Medical Instrument Co., Shanghai, China) will be used with 10-Hz continuous waves, and the current will range from 1 to 5 mA which will be adjusted based on the tolerance of each patient.

### CBT-I treatment

CBT-I will be given while acupuncture treatment is in progress. The intervention will consist of behavioral components (e.g. sleep restriction and stimulus control), cognitive components (e.g., cognitive restructuring and paradoxical intention), progressive muscle relaxation, and sleep hygiene<sup>[29]</sup>.

## Control group

The procedure for the control group will be the same as that for the observation group with no CBT-I treatment. The major difference in interventions between the two groups being the tube needling method, in which no needle will be inserted through the tube for patients in the control group. To mimic the sensation of a real needle being inserted into the body, the acupuncturist will place the tube close to the skin at the acupoint and tap the top of the tube.

## Quality control

The trial will be conducted under the supervision of the First Affiliated Hospital of Sun Yat-sun University. A qualified clinical trial expert will be invited to monitor the study to identify problems during the trial, examine collected data, and control bias.

## Outcome measures

### Primary outcome

Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is an internationally established tool that is used to evaluate sleep quality. The scale includes seven dimensions that consist of subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleeping medication, and daytime dysfunction. The score correlates adversely with sleep quality which a higher score means the sleep quality is worse, and each factor has a score of 0 to 3 to provide a total score of 21 points<sup>[30, 31]</sup>.

### Secondary outcomes

#### The Beck depression inventory

The Beck depression inventory (BDI) is a valid self-assessment index to measure depression severity and consists of 13 items. Each item is scored from 0 to 3 (0 to 4 indicates no depression, 5 to 7 indicates mild depression, 8 to 15 indicates moderate depression), with a score of 16 points or more considered as severe depression<sup>[32-34]</sup>.

#### The Beck anxiety inventory

The Beck anxiety inventory (BAI) is used to assess the degree of anxiety and consists of 21 items scored from 1 to 4 (15 to 25 points indicates mild anxiety, 26 to 35 points indicates moderate anxiety, and 36 points is considered severe anxiety)<sup>[35, 36]</sup>.

#### The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version

The Dysfunctional Beliefs and Attitudes about Sleep Scale 16 version (DBAS-16) is used to evaluate maladaptive cognitions associated with sleep. There are 16 items in the index, which are divided into four factors comprising consequences of insomnia, worry about

Table 2 Acupuncture location and method for each acupoint

| Acupoint             | Location   | Needling method  |
|----------------------|--|--|
| Sishenchong (EX-HN1) | On the parietal region, 1 cun anterior, posterior and lateral to Baihui, 4 acupoints totally.  | The angle between the needle tip and the scalp is 30°. Move the needle tip backward along the anteriore posterior midline, and then insert the needle 0.5 cun. |
| Neiguan(PC6)         | On the line joining Daling and Quze, between the tendons of palmaris longus and flexor carpi radialis, 2 cun above the transverse crease of the wrist. | Puncture perpendicularly 1-1.5 cun.  |
| Taixi (KI3)          | In the depression between the tip of the medial malleolus and the Achilles tendon.   | Puncture perpendicularly 0.5-1 cun.  |
| Shenmen (HT7)        | On the palmar ulnar end of the transverse crease of the wrist, and on the radial aspect of the tendon of the ulnar flexor m. of the wrist.             | Puncture perpendicularly 0.5-1 cun.  |
| Sanyinjiao (SP6)     | Posterior to the mesial border of the tibia, and 3 cun above the tip of the medial malleolus   | Puncture perpendicularly 1-1.5 cun.  |

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4 sleep, sleep expectations, and medication. These factors are scored on a scale of  
5 1–5 (strongly disagree to strongly agree). The total score is positively correlated with the  
6 reasonableness of sleep beliefs and attitudes<sup>[37, 38]</sup>.  
7  
8

### 9 **Sleep staging**

10 The PARADISEP&D9600 (U.S.) Polysomnography Monitoring and Analysis System  
11 will be used to simultaneously monitor EEG, EOG, and EMG. A large clinical dataset of  
12 PSG recordings will be used to train a hybrid convolutional neural network (CNN) and  
13 recurrent neural network (RNN) to learn effective and generalizable features for sleep  
14 stage scoring<sup>[39, 40]</sup>. Then clinical data will be used to identify the deep learning  
15 algorithm. Sleep staging for both datasets will be performed by expert sleep technicians  
16 in nonoverlapping 30-s epochs according to standards by the American Academy of  
17 Sleep Medicine (AASM), as one of five stages: wake (W), non-rapid eye movement (REM)  
18 stage 1 (N1), non-REM stage 2 (N2), non-REM stage 3 (N3), and rapid eye  
19 movement (REM)<sup>[41]</sup>.  
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### 31 **Adverse events**

32 During treatment and four weeks after treatment, a questionnaire will be administered to  
33 evaluate the various discomforts that may be caused by acupuncture: hangover, addiction,  
34 tolerance, fatigue after waking, insomnia rebound, daytime alertness, cognitive function,  
35 and behavior ability.  
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### 41 **Patients and public involvement**

42 Patients and the public are not involved in the design or conduct of the study or the  
43 outcome measures, and no attempt will be made to assess the burden of the intervention  
44 on the patients themselves. The results of this study will be disseminated to study  
45 participants via the website of our hospitals.  
46  
47  
48  
49

### 50 **Statistical analysis**

51 All analyses will be performed on the intention-to-treat population of participants who  
52 had at least one treatment. Missing data will be replaced according to the principle of the  
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4 last observation carried forward. Data analyses will be performed using the SPSS version  
5 25 (IBM Corp.) software. All available data will be analyzed descriptively. For  
6  
7 continuous data, the normality test will be applied at the beginning of the analysis.  
8  
9 Results will be presented as means, standard deviations, and 95% confidence intervals  
10  
11 (CIs) for continuous data that conform to the normal distribution and medians, quartiles,  
12  
13 and ranges for rank data and continuous data that are not normally distributed. Discrete  
14  
15 data will be presented as percentages.  
16

17 We will first examine the descriptive data for sample characteristics at baseline, and  
18  
19 independent samples t-tests will be used to compare groups for continuous variables,  
20  
21 whereas chi-square analysis will be used to compare groups for dichotomous variables.  
22  
23 Second, we will perform two series of repeated-measures and univariate analyses of  
24  
25 covariance (ANCOVA) models to examine treatment effects. We will use  
26  
27 repeated-measures ANCOVAs to analyze the primary and secondary outcome measures  
28  
29 (i.e., PSQI, BDI, BAI, DBAS-16, and sleep staging scores) from pre-treatment to  
30  
31 post-treatment. If a significant effect is observed, we will conduct posthoc paired samples  
32  
33 t-tests to examine within-group changes in study outcomes. For all study outcomes, we  
34  
35 will then perform univariate ANCOVAs to test for group differences in post-treatment  
36  
37 values while controlling for relevant covariates. This process will be repeated to examine  
38  
39 changes in study outcomes from pretreatment to postnatal follow-up.  
40

41 When necessary, ITT analysis and sensitivity analysis will be used to assess the  
42  
43 robustness of the conclusions of the entire clinical trial. To evaluate the consistency of the  
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45 trial and explore the factors that affect efficacy or prognosis, subgroup analysis will be  
46  
47 conducted to identify the population with better efficacy. Safety analysis will be used to  
48  
49 assess the incidence of adverse events and related symptoms in patients with insomnia  
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51 during treatment and follow-up.  
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## Limitations

Currently, CBT-I is recommended as a first-line treatment for insomnia, but it is limited in clinical practice especially in developing countries such as China<sup>[42-45]</sup>. As a complementary alternative therapy with a long history in China, acupuncture has been used as a clinical treatment for insomnia with fewer adverse effects and less permanent damage in previous studies<sup>[13, 14, 16]</sup>. In this study, we will focus on whether electroacupuncture combined with CBT-I could influence sleep quality and sleep architecture, but whether acupuncture therapy alone could influence sleep habits and correct cognition, also sleep architecture worth further research.

During the past decade, there have been various advances in automated sleep staging of PSGs data using the ability of deep learning methods to automatically extract features from data that are relevant to the classification, moreover, the performance of deep neural networks continues to improve as datasets become larger<sup>[46-50]</sup>. To analyze the effects of electroacupuncture combined with CBT-I on sleep architecture, deep learning will be used to analyze PSGs in various clinical settings in this study. But due to lack of acceptability among patients, some of the participants received placebo treatment will drop, which may make analyses no meaningful due to the small number of participants in each arm. Notwithstanding, we will be able to optimize the randomized design and statistical analysis to avoid systematic errors and minimize the bias.

## Ethics and dissemination

This trial has been approved by the institutional review boards and ethics committees of the First Affiliated Hospital of Sun Yat-sun University (2021763). The results will be disseminated through peer-reviewed journals. The results of this trial will be disseminated through peer-reviewed publications and conference abstracts or posters.

## Acknowledgments

Not applicable.

## Footnotes

Contributors: Wenya Pei and Te He designed the trial protocol and drafted the manuscript. Liming Lu, Jingwen Ruan, and Guihua Wen revised the manuscript. Pei Yang, Xiaozhou Lv, and Boyu Jiao will plan the data analysis. Liqian Cui, Yingshuo Yan, Fanqi Meng, Guanheng He, and Xin Zhou will participate in participant recruitment. All authors discussed, read, and revised the manuscript, and all approved the publication of this protocol.

Funding: The study was supported by the Key R&D Program of Guangdong Province (2020B1111120001).

Competing interests: None declared.

Patient consent for publication: Not applicable

Provenance and peer review: Not commissioned; externally peer-reviewed.

## Ethics statements

Patient consent for publication

Not applicable.

Ethics approval and consent to participate: The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sun University (2021763).

Participants will be included only after they provide written informed consent. The study was registered in the Chinese Clinical Trial Registry (No.ChiCTR2100052502, 30/10/2021).

## References

1. Riemann D, Benz F, Dressle RJ, Espie CA, Johann AF, Blanken TF, Leerssen J, Wassing R, Henry AL, Kyle SD et al: Insomnia disorder: State of the science and challenges for the future. *Journal of sleep research* 2022, 31(4):e13604.
2. Chan WS, Levensen MP, McCrae CS: A meta-analysis of associations between obesity and insomnia diagnosis and symptoms. *Sleep medicine reviews* 2018, 40:170-182.
3. Wickwire EM: The Value of Digital Insomnia Therapeutics: What We Know and What We Need To Know. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine* 2019, 15(1):11-13.
4. Kalmbach DA, Anderson JR, Drake CL: The impact of stress on sleep: Pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. *Journal of sleep research* 2018, 27(6):e12710.
5. Shekleton JA, Flynn-Evans EE, Miller B, Epstein LJ, Kirsch D, Brogna LA, Burke LM, Bremer E, Murray JM, Gehrman P et al: Neurobehavioral performance impairment in insomnia: relationships with self-reported sleep and daytime functioning. *Sleep* 2014, 37(1):107-116.
6. Cross NE, Carrier J, Postuma RB, Gosselin N, Kakinami L, Thompson C, Chouchou F, Dang-Vu TT: Association between insomnia disorder and cognitive function in middle-aged and older adults: a cross-sectional analysis of the Canadian Longitudinal Study on Aging. *Sleep* 2019, 42(8).
7. Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML, Bixler EO: Risk factors for incident chronic insomnia: a general population prospective study. *Sleep medicine* 2012, 13(4):346-353.
8. Zhang Y, Ren R, Lei F, Zhou J, Zhang J, Wing YK, Sanford LD, Tang X: Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A systematic review and meta-analysis. *Sleep medicine reviews* 2019, 45:1-17.

- 1  
2  
3  
4 9. Kessler RC, Berglund PA, Coulouvrat C, Fitzgerald T, Hajak G, Roth T, Shahly V,  
5  
6 Shillington AC, Stephenson JJ, Walsh JK: Insomnia, comorbidity, and risk of injury  
7  
8 among insured Americans: results from the America Insomnia Survey. *Sleep* 2012,  
9  
10 35(6):825-834.
- 11  
12 10. Kalmbach DA, Cheng P, Arnedt JT, Cuamatzi-Castelan A, Atkinson RL,  
13  
14 Fellman-Couture C, Roehrs T, Drake CL: Improving Daytime Functioning, Work  
15  
16 Performance, and Quality of Life in Postmenopausal Women With Insomnia: Comparing  
17  
18 Cognitive Behavioral Therapy for Insomnia, Sleep Restriction Therapy, and Sleep  
19  
20 Hygiene Education. *Journal of clinical sleep medicine : JCSM : official publication of the*  
21  
22 *American Academy of Sleep Medicine* 2019, 15(7):999-1010.
- 23  
24 11. Espie CA, Emsley R, Kyle SD, Gordon C, Drake CL, Siriwardena AN, Cape J, Ong  
25  
26 JC, Sheaves B, Foster R et al: Effect of Digital Cognitive Behavioral Therapy for  
27  
28 Insomnia on Health, Psychological Well-being, and Sleep-Related Quality of Life: A  
29  
30 Randomized Clinical Trial. *JAMA psychiatry* 2019, 76(1):21-30.
- 31  
32 12. Thakral M, Von Korff M, McCurry SM, Morin CM, Vitiello MV: Changes in  
33  
34 dysfunctional beliefs about sleep after cognitive behavioral therapy for insomnia: A  
35  
36 systematic literature review and meta-analysis. *Sleep medicine reviews* 2020, 49:101230.
- 37  
38 13. Garland SN, Xie SX, DuHamel K, Bao T, Li Q, Barg FK, Song S, Kantoff P,  
39  
40 Gehrman P, Mao JJ: Acupuncture Versus Cognitive Behavioral Therapy for Insomnia in  
41  
42 Cancer Survivors: A Randomized Clinical Trial. *Journal of the National Cancer Institute*  
43  
44 2019, 111(12):1323-1331.
- 45  
46 14. Liou KT, Root JC, Garland SN, Green J, Li Y, Li QS, Kantoff PW, Ahles TA, Mao  
47  
48 JJ: Effects of acupuncture versus cognitive behavioral therapy on cognitive function in  
49  
50 cancer survivors with insomnia: A secondary analysis of a randomized clinical trial.  
51  
52 *Cancer* 2020, 126(13):3042-3052.
- 53  
54 15. Xing J, Wu X, Liu H, Wang J, Jiang S, Lozada A, Wang Y: Effects of  
55  
56 Electroacupuncture Therapy and Cognitive Behavioral Therapy in Chronic Insomnia: A  
57  
58  
59  
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1  
2  
3  
4 Randomized Controlled Study. Evidence-based complementary and alternative medicine :  
5 eCAM 2020, 2020:5630130.  
6

7 16. Cui L, Jingwen R, Minying Z, Guanheng H, Hao L: Effects of acupuncture combined  
8 with cognitive behavioral therapy on sleep quality, sleep belief and attitude in patients  
9 with chronic insomnia. Guangdong Medical Journal 2020, 41(10):1005-1009.  
10  
11

12 17. Ruan JW, Wang CH, Liao XX, Yan YS, Hu YH, Rao ZD, Wen M, Zeng XX, Lai  
13 XX: Electroacupuncture treatment of chronic insomniacs. Chin Med J (Engl) 2009,  
14 122(23):2869-2873.  
15  
16

17 18. Yin X, Gou M, Xu J, Dong B, Yin P, Masquelin F, Wu J, Lao L, Xu S: Efficacy and  
18 safety of acupuncture treatment on primary insomnia: a randomized controlled trial.  
19 Sleep medicine 2017, 37:193-200.  
20  
21

22 19. Pei W, Peng R, Gu Y, Zhou X, Ruan J: Research trends of acupuncture therapy on  
23 insomnia in two decades (from 1999 to 2018):a bibliometric analysis. BMC  
24 complementary and alternative medicine 2019, 19(1):225.  
25  
26

27 20. Gorban AN, Makarov VA, Tyukin IY: The unreasonable effectiveness of small  
28 neural ensembles in high-dimensional brain. Physics of life reviews 2019, 29:55-88.  
29  
30

31 21. Bresch E, Großekathöfer U, Garcia-Molina G: Recurrent Deep Neural Networks for  
32 Real-Time Sleep Stage Classification From Single Channel EEG. Frontiers in  
33 computational neuroscience 2018, 12:85.  
34  
35

36 22. Hassan AR, Bhuiyan MIH: Automated identification of sleep states from EEG  
37 signals by means of ensemble empirical mode decomposition and random under sampling  
38 boosting. Computer methods and programs in biomedicine 2017, 140:201-210.  
39  
40

41 23. Schulz KF, Altman DG, Moher D: CONSORT 2010 statement: updated guidelines  
42 for reporting parallel group randomised trials. BMJ (Clinical research ed) 2010,  
43 340:c332.  
44  
45

46 24. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A,  
47 Moher D: Revised STandards for Reporting Interventions in Clinical Trials of  
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3  
4 Acupuncture (STRICTA): Extending the CONSORT statement. *Journal of*  
5 *evidence-based medicine* 2010, 3(3):140-155.
- 6  
7  
8 25. Wang C, Yang WJ, Yu XT, Fu C, Li JJ, Wang J, Xu WL, Zheng YX, Chen XY,  
9  
10 Chen YF: Acupuncture for insomnia with short sleep duration: protocol for a randomised  
11 controlled trial. *BMJ open* 2020, 10(3):e033731.
- 12  
13 26. Battle DE: *Diagnostic and Statistical Manual of Mental Disorders (DSM)*. CoDAS  
14 2013, 25(2):191-192.
- 15  
16  
17 27. Sateia MJ: *International classification of sleep disorders-third edition: highlights and*  
18 *modifications*. *Chest* 2014, 146(5):1387-1394.
- 19  
20  
21 28. Cui, L, Ruan, J, Zheng, M, He, G, Li H: Effects of acupuncture combined  
22 with cognitive behavioral therapy on sleep quality, sleep belief and attitude in patients  
23 with chronic insomnia. *Guangdong Medical Journal* 2020, 41(10):1005-1009.
- 24  
25  
26 29. Qaseem A, Kansagara D, Forcica MA, Cooke M, Denberg TD: *Management of*  
27 *Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American*  
28 *College of Physicians*. *Annals of internal medicine* 2016, 165(2):125-133.
- 29  
30  
31 30. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ: *The Pittsburgh*  
32 *Sleep Quality Index: a new instrument for psychiatric practice and research*. *Psychiatry*  
33 *research* 1989, 28(2):193-213.
- 34  
35  
36 31. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A:  
37 *The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and*  
38 *non-clinical samples: A systematic review and meta-analysis*. *Sleep medicine reviews*  
39 2016, 25:52-73.
- 40  
41  
42 32. Robinson BE, Kelley L: *Concurrent validity of the Beck Depression Inventory as a*  
43 *measure of depression*. *Psychological reports* 1996, 79(3 Pt 1):929-930.
- 44  
45  
46 33. Piotrowski C: *Use of the Beck Depression Inventory in clinical practice*.  
47 *Psychological reports* 1996, 79(3 Pt 1):873-874.
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4 34. Carney CE, Ulmer C, Edinger JD, Krystal AD, Knauss F: Assessing depression  
5 symptoms in those with insomnia: an examination of the beck depression inventory  
6 second edition (BDI-II). *Journal of psychiatric research* 2009, 43(5):576-582.  
7  
8  
9 35. Beck AT, Epstein N, Brown G, Steer RA: An inventory for measuring clinical  
10 anxiety: psychometric properties. *Journal of consulting and clinical psychology* 1988,  
11 56(6):893-897.  
12  
13 36. Nyer M, Farabaugh A, Fehling K, Soskin D, Holt D, Papakostas GI, Pedrelli P, Fava  
14 M, Pisoni A, Vitolo O et al: Relationship between sleep disturbance and depression,  
15 anxiety, and functioning in college students. *Depression and anxiety* 2013,  
16 30(9):873-880.  
17  
18 37. Morin CM, Vallières A, Ivers H: Dysfunctional beliefs and attitudes about sleep  
19 (DBAS): validation of a brief version (DBAS-16). *Sleep* 2007, 30(11):1547-1554.  
20  
21 38. Chung KF, Ho FY, Yeung WF: Psychometric Comparison of the Full and  
22 Abbreviated Versions of the Dysfunctional Beliefs and Attitudes about Sleep Scale.  
23 *Journal of clinical sleep medicine : JCSM : official publication of the American Academy*  
24 *of Sleep Medicine* 2016, 12(6):821-828.  
25  
26 39. Ramaswamy SM, Weerink MAS, Struys M, Nagaraj SB: Dexmedetomidine-induced  
27 deep sedation mimics non-rapid eye movement stage 3 sleep: large-scale validation using  
28 machine learning. *Sleep* 2021, 44(2).  
29  
30 40. Abou Jaoude M, Sun H, Pellerin KR, Pavlova M, Sarkis RA, Cash SS, Westover MB,  
31 Lam AD: Expert-level automated sleep staging of long-term scalp  
32 electroencephalography recordings using deep learning. *Sleep* 2020, 43(11).  
33  
34 41. Malhotra RK, Kirsch DB, Kristo DA, Olson EJ, Aurora RN, Carden KA, Chervin  
35 RD, Martin JL, Ramar K, Rosen CL et al: Polysomnography for Obstructive Sleep Apnea  
36 Should Include Arousal-Based Scoring: An American Academy of Sleep Medicine  
37 Position Statement. *Journal of clinical sleep medicine : JCSM : official publication of the*  
38 *American Academy of Sleep Medicine* 2018, 14(7):1245-1247.  
39  
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4 42. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groseelj L, Ellis JG, Espie  
5 CA, Garcia-Borreguero D, Gjerstad M, Gonçalves M et al: European guideline for the  
6 diagnosis and treatment of insomnia. *Journal of sleep research* 2017, 26(6):675-700.  
7  
8  
9 43. Kathol RG, Arnedt JT: Cognitive Behavioral Therapy for Chronic Insomnia:  
10 Confronting the Challenges to Implementation. *Annals of internal medicine* 2016,  
11 165(2):149-150.  
12  
13  
14 44. Ree M, Junge M, Cunningham D: Australasian Sleep Association position statement  
15 regarding the use of psychological/behavioral treatments in the management of insomnia  
16 in adults. *Sleep medicine* 2017, 36 Suppl 1:S43-s47.  
17  
18  
19 45. Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia  
20 MJ, Troxel WM, Zhou ES, Kazmi U et al: Behavioral and psychological treatments for  
21 chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical  
22 practice guideline. *Journal of clinical sleep medicine : JCSM : official publication of the*  
23 *American Academy of Sleep Medicine* 2021, 17(2):255-262.  
24  
25  
26 46. Zhang L, Fabbri D, Upender R, Kent D: Automated sleep stage scoring of the Sleep  
27 Heart Health Study using deep neural networks. *Sleep* 2019, 42(11).  
28  
29  
30 47. Feige B, Baumgartner B, Meyer D, Riemann D: The Relationship Between PSG and  
31 Morning/Evening Emotional Parameters in Patients With Insomnia Disorder and Good  
32 Sleepers. *Frontiers in psychology* 2018, 9:2712.  
33  
34  
35 48. Lajnef T, Chaibi S, Ruby P, Aguera PE, Eichenlaub JB, Samet M, Kachouri A, Jerbi  
36 K: Learning machines and sleeping brains: Automatic sleep stage classification using  
37 decision-tree multi-class support vector machines. *Journal of neuroscience methods* 2015,  
38 250:94-105.  
39  
40  
41 49. Qu W, Wang Z, Hong H, Chi Z, Feng DD, Grunstein R, Gordon C: A Residual  
42 Based Attention Model for EEG Based Sleep Staging. *IEEE journal of biomedical and*  
43 *health informatics* 2020, 24(10):2833-2843.  
44  
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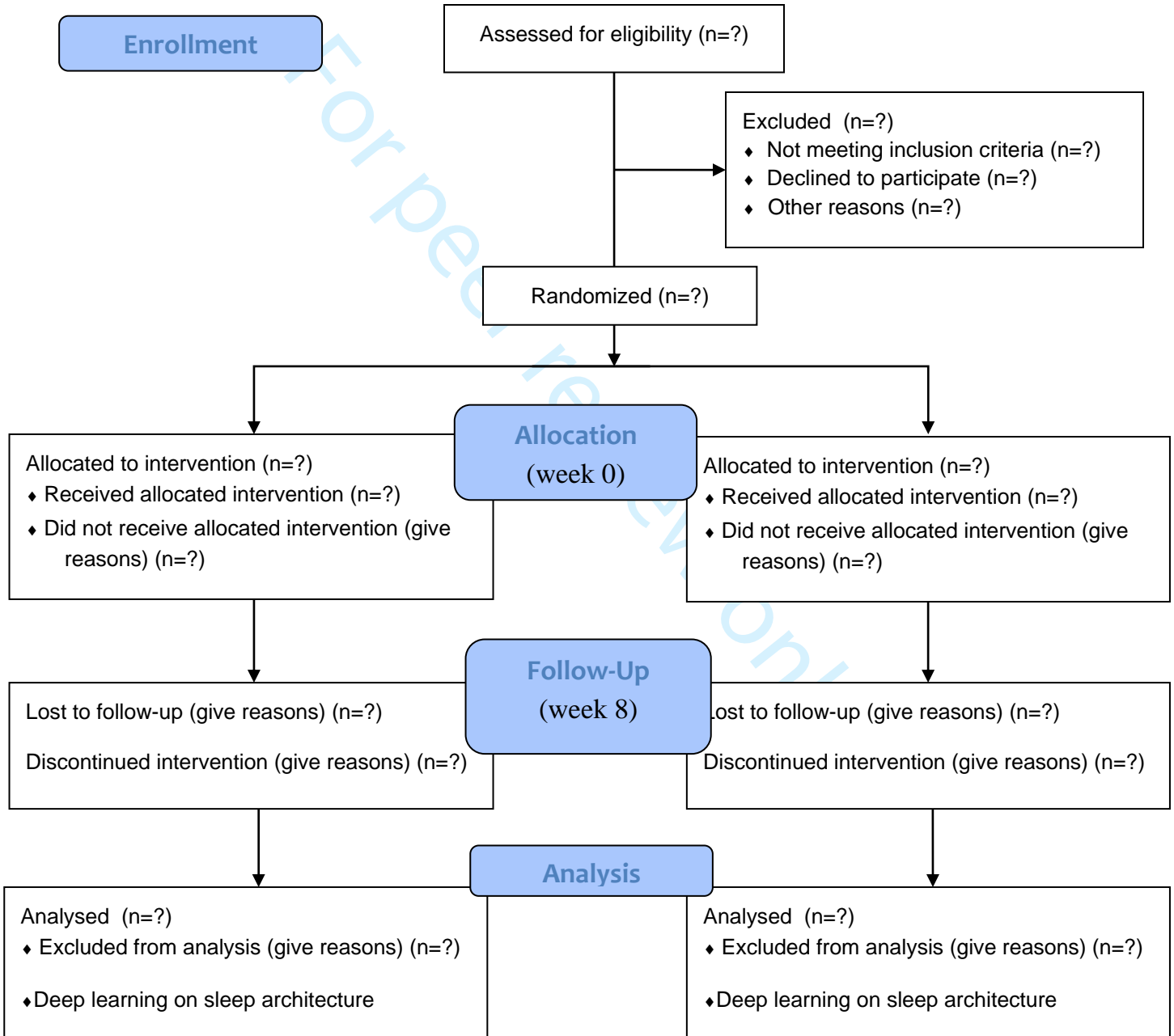
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4 50. Wang Y, Loparo KA, Kelly MR, Kaplan RF: Evaluation of an automated  
5 single-channel sleep staging algorithm. *Nature and science of sleep* 2015, 7:101-111.  
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23 Fig 1. CONSORT 2010 Flow Diagram

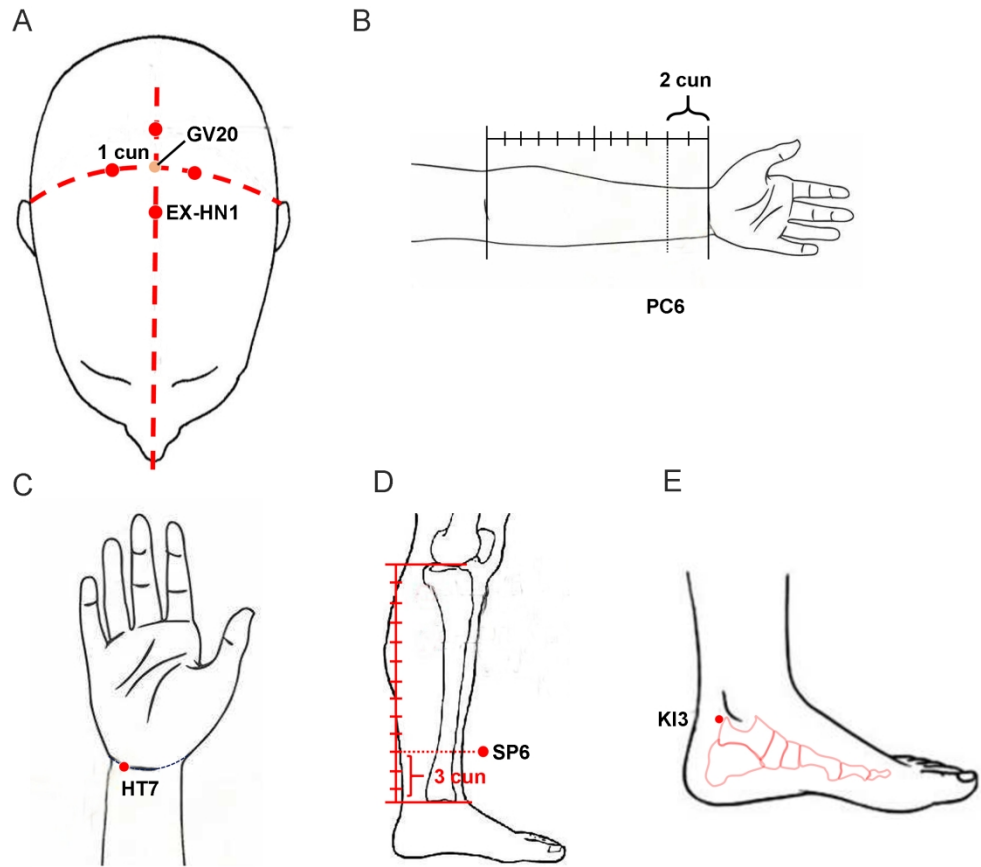
24 Fig 2. Location of acupoints  
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**CONSORT 2010 Flow Diagram**



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location of accupoints

209x202mm (300 x 300 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item                      | Item No | Description  | Addressed on page number |
|-----------------------------------|---------|--|--------------------------|
| <b>Administrative information</b> |         |  |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym   | <u>1</u>                 |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry   | <u>1</u>                 |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set   | <u>1</u>                 |
| Protocol version                  | 3       | Date and version identifier  | <u>1</u>                 |
| Funding                           | 4       | Sources and types of financial, material, and other support  | <u>12</u>                |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors  | <u>1,12</u>              |
|                                   | 5b      | Name and contact information for the trial sponsor   | <u>12</u>                |
|                                   | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | <u>12</u>                |
|                                   | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)                         | <u>NA</u>                |

|    |   |     |  |                           |
|----|---|-----|--|---------------------------|
| 1  | <b>Introduction</b>                                       |     |  |                           |
| 2  |   |     |  |                           |
| 3  | Background and rationale                                  | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention   | <u>3-4</u>                |
| 4  |   |     |  |                           |
| 5  |   |     |  |                           |
| 6  |   | 6b  | Explanation for choice of comparators  | <u>5</u>                  |
| 7  |   |     |  |                           |
| 8  | Objectives  | 7   | Specific objectives or hypotheses  | <u>4</u>                  |
| 9  |   |     |  |                           |
| 10 | Trial design  | 8   | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)  | <u>4</u>                  |
| 11 |   |     |  |                           |
| 12 |   |     |  |                           |
| 13 |   |     |  |                           |
| 14 | <b>Methods: Participants, interventions, and outcomes</b> |     |  |                           |
| 15 |   |     |  |                           |
| 16 | Study setting   | 9   | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained   | <u>4-5</u>                |
| 17 |   |     |  |                           |
| 18 |   |     |  |                           |
| 19 | Eligibility criteria                                      | 10  | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)   | <u>6</u>                  |
| 20 |   |     |  |                           |
| 21 |   |     |  |                           |
| 22 | Interventions   | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered   | <u>6-7</u>                |
| 23 |   |     |  |                           |
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| 25 |   |     |  |                           |
| 26 |   | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)   | <u>6</u>                  |
| 27 |   |     |  |                           |
| 28 |   |     |  |                           |
| 29 |   | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)  | <u>6</u>                  |
| 30 |   |     |  |                           |
| 31 |   |     |  |                           |
| 32 |   | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial  | <u>6</u>                  |
| 33 |   |     |  |                           |
| 34 | Outcomes  | 12  | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | <u>7-9</u>                |
| 35 |   |     |  |                           |
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| 39 |   |     |  |                           |
| 40 | Participant timeline                                      | 13  | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)   | <u>4,Table 1,Figure 1</u> |
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|   |             |    |   |            |
|---|-------------|----|---|------------|
| 1 | Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |            |
| 2 |             |    |   |            |
| 3 |             |    |   |            |
| 4 | Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size   | <u>8-9</u> |
| 5 |             |    |   |            |

**Methods: Assignment of interventions (for controlled trials)**

|    |                                  |     |  |          |
|----|----------------------------------|-----|--|----------|
| 8  | Allocation:                      |     |  | <u>5</u> |
| 9  |                                  |     |  |          |
| 10 | Sequence generation              | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | <u>5</u> |
| 11 |                                  |     |  |          |
| 12 |                                  |     |  |          |
| 13 |                                  |     |  |          |
| 14 |                                  |     |  |          |
| 15 |                                  |     |  |          |
| 16 | Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned  | <u>5</u> |
| 17 |                                  |     |  |          |
| 18 |                                  |     |  |          |
| 19 |                                  |     |  |          |
| 20 | Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions  | <u>5</u> |
| 21 |                                  |     |  |          |
| 22 |                                  |     |  |          |
| 23 |                                  |     |  |          |
| 24 | Blinding (masking)               | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how  | <u>5</u> |
| 25 |                                  |     |  |          |
| 26 |                                  |     |  |          |
| 27 |                                  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial   | <u>5</u> |
| 28 |                                  |     |  |          |
| 29 |                                  |     |  |          |
| 30 |                                  |     |  |          |

**Methods: Data collection, management, and analysis**

|    |                         |     |  |          |
|----|-------------------------|-----|--|----------|
| 31 |                         |     |  |          |
| 32 |                         |     |  |          |
| 33 | Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | <u>9</u> |
| 34 |                         |     |  |          |
| 35 |                         |     |  |          |
| 36 |                         |     |  |          |
| 37 |                         |     |  |          |
| 38 |                         |     |  |          |
| 39 |                         |     |  |          |
| 40 |                         | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols  | <u>9</u> |
| 41 |                         |     |  |          |
| 42 |                         |     |  |          |

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|    |                                 |     |   |             |
|----|---------------------------------|-----|---|-------------|
| 1  | Data management                 | 19  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol   | <u>9-10</u> |
| 2  |                                 |     |   |             |
| 3  |                                 |     |   |             |
| 4  |                                 |     |   |             |
| 5  | Statistical methods             | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol  | <u>9-10</u> |
| 6  |                                 |     |   |             |
| 7  |                                 |     |   |             |
| 8  |                                 | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | <u>9-19</u> |
| 9  |                                 |     |   |             |
| 10 |                                 | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)   | <u>9-10</u> |
| 11 |                                 |     |   |             |
| 12 |                                 |     |   |             |
| 13 |                                 |     |   |             |
| 14 | <b>Methods: Monitoring</b>      |     |   |             |
| 15 |                                 |     |   |             |
| 16 | Data monitoring                 | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | <u>9-10</u> |
| 17 |                                 |     |   |             |
| 18 |                                 |     |   |             |
| 19 |                                 |     |   |             |
| 20 |                                 |     |   |             |
| 21 |                                 |     |   |             |
| 22 |                                 | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial   | <u>9-10</u> |
| 23 |                                 |     |   |             |
| 24 |                                 |     |   |             |
| 25 | Harms                           | 22  | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct   | <u>9-10</u> |
| 26 |                                 |     |   |             |
| 27 |                                 |     |   |             |
| 28 | Auditing                        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor   | <u>9-10</u> |
| 29 |                                 |     |   |             |
| 30 |                                 |     |   |             |
| 31 |                                 |     |   |             |
| 32 | <b>Ethics and dissemination</b> |     |   |             |
| 33 |                                 |     |   |             |
| 34 | Research ethics approval        | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval   | <u>5</u>    |
| 35 |                                 |     |   |             |
| 36 |                                 |     |   |             |
| 37 | Protocol amendments             | 25  | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)  | <u>NA</u>   |
| 38 |                                 |     |   |             |
| 39 |                                 |     |   |             |
| 40 |                                 |     |   |             |
| 41 |                                 |     |   |             |
| 42 |                                 |     |   |             |
| 43 |                                 |     |   |             |
| 44 |                                 |     |   |             |
| 45 |                                 |     |   |             |
| 46 |                                 |     |   |             |



|    |                               |     |  |   |
|----|-------------------------------|-----|--|---|
| 1  | Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)   | 6                                       |
| 2  |                               |     |  |   |
| 3  |                               |     |  |   |
| 4  |                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable  | 6                                       |
| 5  |                               |     |  |   |
| 6  |                               |     |  |   |
| 7  | Confidentiality               | 27  | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial   | 6                                       |
| 8  |                               |     |  |   |
| 9  |                               |     |  |   |
| 10 | Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site  | 12                                      |
| 11 |                               |     |  |   |
| 12 |                               |     |  |   |
| 13 | Access to data                | 29  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators  | 6                                       |
| 14 |                               |     |  |   |
| 15 |                               |     |  |   |
| 16 | Ancillary and post-trial care | 30  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  | 6                                       |
| 17 |                               |     |  |   |
| 18 |                               |     |  |   |
| 19 |                               |     |  |   |
| 20 | Dissemination policy          | 31a | Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 6                                       |
| 21 |                               |     |  |   |
| 22 |                               |     |  |   |
| 23 |                               |     |  |   |
| 24 |                               | 31b | Authorship eligibility guidelines and any intended use of professional writers   | 6                                       |
| 25 |                               |     |  |   |
| 26 |                               | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code  | 6                                       |
| 27 |                               |     |  |   |
| 28 |                               |     |  |   |
| 29 |                               |     |  |   |
| 30 | <b>Appendices</b>             |     |  |   |
| 31 |                               |     |  |   |
| 32 | Informed consent materials    | 32  | Model consent form and other related documentation given to participants and authorised surrogates   | <u>See The Ethics Approval Document</u> |
| 33 |                               |     |  |   |
| 34 |                               |     |  |   |
| 35 |                               |     |  |   |
| 36 |                               |     |  |   |
| 37 | Biological specimens          | 33  | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable   | <u>NA</u>                               |
| 38 |                               |     |  |   |
| 39 |                               |     |  |   |

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\*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. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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