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# Acupuncture for Insomnia with Short Sleep Duration: Protocol for a Randomized Controlled Trial



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# Acupuncture for Insomnia with Short Sleep Duration: Protocol for a Randomized Controlled Trial

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## Abstract

**Introduction:** Insomnia with short sleep duration has a more serious negative impact on patient health. The existing literature suggests that medication therapy is more effective for this phenotype of insomnia compared to cognitive behavioural therapy (CBT). However, the potential side effects of hypnotic medications hinder their clinical application. Acupuncture has been widely used in the treatment of insomnia, but it remains unclear whether it has therapeutic efficacy for insomnia with short sleep duration. The purpose of this trial is to evaluate the efficacy and safety of acupuncture for insomnia with short sleep duration.

**Methods and analysis:** This study is designed as a randomized, single centre, single-blinded, placebo acupuncture controlled trial involving 152 participants. Eligible patients will be divided into two groups according to the objective total sleep time: insomnia with normal sleep duration group and insomnia with short sleep duration group. Then, patients in each group will be randomly assigned to two subgroups, the treatment group (acupuncture) and the control group (placebo acupuncture), in a 1:1 ratio with 38 subjects in each subgroup. The primary outcome is the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). Secondary outcomes are

actigraphy (ACT), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI) and the Fatigue Severity Scale (FSS). All adverse effects will be assessed by the Treatment Emergent Symptom Scale. Outcomes will be evaluated at baseline, post-treatment, as well as at 1-week and 1-month follow-up.

**Ethics and dissemination:** This protocol has been approved by the ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (No.: 2019-17). Written informed consent will be obtained from all participants. The results will be disseminated through peer-reviewed journals for publications.

**Registration:** ChiCTR1900023473; Pre-results.

**Keywords** Acupuncture; Insomnia; Short Sleep Duration; Randomized controlled trial; Protocol.

## Article Summary

## Strengths and limitations of this study

1. This is the first randomized, single centre, placebo acupuncture controlled trial to study the efficacy and safety of acupuncture for insomnia with short sleep duration.
2. Through a 2×2 factorial design, this trial will study whether the efficacy of acupuncture on chronic insomnia is related to insomnia phenotypes or acupoint effects and will evaluate both subjective and objective parameters.
3. The results of this study will provide knowledge relevant for clinical practice and fill gaps in current guidelines concerning acupuncture for insomnia with short sleep duration.
4. One limitation is that this study is implemented in only one center in Chinese subjects and without long-term treatment and follow-up, which may limit its generalisability.

# 1. Introduction

In recent years, the incidence of chronic insomnia in adults has become higher [1], and short sleepers are also showing an increasing trend [2]. Studies have found that patients with insomnia accompanied by short sleep duration can cause many chronic diseases, such as obesity, diabetes, cardiovascular disease, chronic kidney disease, and hypertension [3-7], and may even result in inadequate hydration [8]. Similarly, insomnia patients who are accompanied by short sleep duration will have many adverse effects on their health. Some researchers have found that the mortality rate of insomnia patients is three times more than that of people without insomnia. When patients with insomnia have short sleep duration, the damage to their health will be more serious and the mortality rate will be higher [9].

Based on this, Vgontzas [10] proposed that insomnia can be divided into two phenotypes based on objective sleep duration, with the threshold of the total sleep time being 6 h. The first phenotype (short objective sleep duration) is characterized by physiological hyperarousal with numerous medical complications. The second phenotype (normal sleep duration) is characterized by cognitive-emotional disorders, accompanied by a process of cortical excitement and remitting course. Vgontzas also suggested that insomnia with short sleep duration may be less sensitive to CBT-I therapy. Although many guidelines of sleep disorders recommend CBT-I as the primary treatment [11-13], Christina J and her team conducted a trial and concluded that insomnia with short sleep duration has a dull response to CBT-I therapy [14].

Because CBT-I lacks specificity for the treatment of insomnia with objective short sleep duration, these patients can only resort to sleep medicine. However, there are many side effects to benzodiazepine receptor agonists, such as hangover effects, cognitive impairment, and drug addiction [15-16]. Therefore, many people with insomnia seek complementary and alternative medicine, such as acupuncture. Acupuncture has been widely used in the treatment of insomnia, and studies have shown that it can improve sleep efficiency, daytime functioning, psychological health and sleep quality of insomnia subjects [17-18]. Our previous research also showed that acupuncture has a

good short-term effect on perimenopausal insomnia [19]. An earlier Cochrane review showed that acupuncture can improve the sleep quality of insomnia subjects compared with untreated groups and placebo acupuncture groups [20].

This is the first rigorous randomized controlled clinical trial to study the therapeutic effect of acupuncture on insomnia with short sleep duration and compare the effects on different insomnia phenotypes. Our objectives are as follows: (1) In randomized controlled trials with a 2×2 factorial design, we will study whether the clinical effect of acupuncture on chronic insomnia is related to insomnia phenotypes or acupoint effects and will evaluate both subjective and objective parameters. (2) We will explore the clinical symptomatic manifestations (difficulty in falling asleep, early awakening, difficulty in maintaining sleep, etc.) and psychological characteristics (anxiety, depression, sensitivity, etc.) and analyse the acupuncture effect for these symptoms of insomnia with short sleep duration.

# 2. Methods

## 2.1. Study design

This study is a randomized controlled trial with a single-centre, single-blind, 2×2 factorial design and will be completed in Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. The study period will be from November 2019 to April 2021, and the Shanghai Municipal Commission of Health and Family Planning will be the management organization of the study.

Insomnia subjects who meet the inclusion criteria will be divided into two groups according to the objective total sleep time (TST): insomnia with a short sleep duration group (objective sleep time < 6 h) and insomnia with a normal sleep duration group (objective sleep time ≥ 6 h). A total of 76 subjects will be recruited from each group. Each group will be randomly assigned to the acupuncture subgroup and the placebo acupuncture subgroup at a 1:1 ratio. Each subject will experience screening, treatment and a follow-up period of approximately 8 weeks. All subjects will complete the

following scales [21]: The Pittsburgh Sleep Quality Index (PSQI) [22] and the Insomnia Severity Index (ISI) [23-24] will evaluate subjects' subjective sleep improvement. Subjects will be assessed for the objective total sleep time by actigraphy [25] in conjunction with a sleep diary [26]. Subjects' mood improvement will be evaluated by the Beck Anxiety Inventory (BAI) [27] and the Beck Depression Inventory (BDI) [28]. The Fatigue Severity Scale (FSS) [29] will be used to assess the improvement in fatigue. The above scales or actigraphy will be evaluated during the screening period and after the treatment at one-week and one-month follow-ups (Figure 1). Subjects will sign the informed consent form after enrolment.

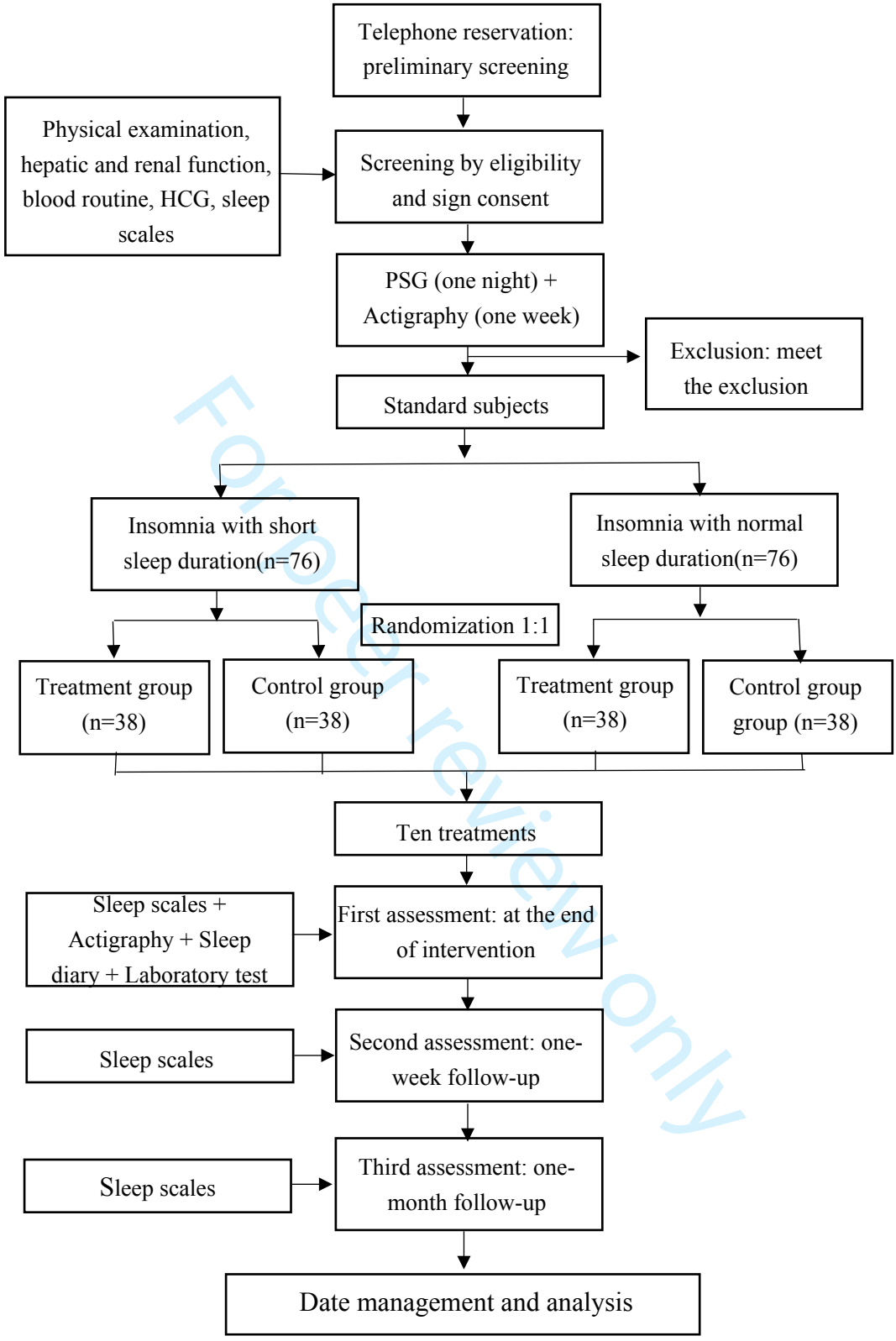


Fig.1. Trial flow chart

## 2.2. Participants

The study will include 152 insomnia participants. We plan to recruit participants in multiple ways, and the recruitment location will be restricted to Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine, Shanghai, China. Our hospital is a comprehensive tertiary hospital with clinical treatment, scientific research and teaching practice. The main source of the subjects will be the outpatients who meet our criteria. In addition, we will also recruit participants through newspapers, social media and advertising. The time limit will be from November 2019 to April 2021. The site of our clinical trial will be the Insomnia Diagnosis and Treatment Center of the Acupuncture and Moxibustion Department at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. All participants who are willing to participate in the trial will be required to call our research coordinator and arrange an outpatient interview on the first available date.

### 2.2.1. Inclusion criteria

The outpatient interview will be conducted in the form of a semi-structured interview questionnaire, which will contain the cause of insomnia, onset process, treatment process, main sleep complaints, bedtime status, sleep-wake cycle, other sleep-related symptoms, daytime symptoms, mental state, etc. [30]. The inclusion criteria have been developed based on the diagnostic criteria for chronic insomnia in the International Classification of Sleep Disorders (Third Edition) (ICSD-3) [31] developed by the American Academy of Sleep Medicine in 2014. The inclusion criteria are as follows:

(1) Between 18 and 65 years of age;

(2) Compliance with the diagnostic criteria for chronic insomnia in ICSD-3;

(3) Stable administration of sedative-hypnotic drugs for more than 3 months before entering the study or not taking such drugs;

(4) PSQI [22] > 5 points, ISI [23-24] > 14 points, BAI [27] < 45 points and BDI [28] ≤ 28 points;

(5) Never received acupuncture treatment;

(6) Voluntarily participated in the study and signed informed consent.

In addition, all participants will complete a one-week sleep actigraphy and diary to determine their sleep patterns and objective sleep duration before enrolment [32]. We will recruit 76 subjects in each group (insomnia with short sleep duration and insomnia with normal sleep duration). If one group completes recruitment first, that specific group will stop recruiting.

**2.2.2. Exclusion criteria**

The exclusion criteria are as follows:

(1) Severe hepatic and renal function damage, as well as haematologic diseases and respiratory diseases and diagnosis of mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [33];

(2) Semi-structured clinical interviews determine subjects have other sleep disorders rather than primary insomnia;

(3) Infectious diseases such as infectious hepatitis, tuberculosis, AIDS, and syphilis;

(4) Severe digestive system diseases and severe malnutrition;

(5) Pregnant or lactating;

(6) Severe trauma with no cure or not suitable for acupuncture, such as allergic constitution and severe dermatosis;

(7) An apnoea–hypopnea index (AHI) >10 or periodic limb movements index during sleep associated with >15 arousals per hour on diagnostic PSG [34];

(8) Participated in other clinical trials in the last 3 months.

## 2.3. Interventions

The acupuncturist for this study has received a master's degree in acupuncture and tuina at Shanghai University of Traditional Chinese Medicine, has 8 years of training experience, has obtained a doctor qualification certificate, and has 3 years of clinical work experience. All study participants will receive 10 days of training prior to the start of the trial to become more familiar with the process.

The subjects in the acupuncture group will be placed in the supine position. We have selected 5 acupoints for this study: GV20 (Baihui), PC 6 (Neiguan), SP 6 (Sanyinjiao),

HT 7 (Shenmen) and Ex-HN 1 (Sishencong). The reason for choosing these acupoints is the previous systematic review [35-36] and our clinical experience. A disposable sterile stainless steel acupuncture needle with a length of 40 mm and a diameter of 0.25 mm will be used (Andy, Guizhou, China). The acupuncturist will take the points on both sides of the body. The needle will be inserted into the skin to a depth of 10-20 mm, which is determined by the acupuncturist according to body type (high or short, fat or thin). After piercing, a thrusting and twirling of the needle will be performed to induce the sensation of "De qi", and the needle will be left for 20 minutes [37]. "De qi" means that after the needle has penetrated into the acupoint to a certain depth, the needle is thrust and twirled to cause the acupoint to obtain the induction of meridian qi. The subjects will have a self-conscious reaction such as soreness, heaviness or distention. This is the key process in acupuncture treatment [38].

Subjects who entered the control group will receive a placebo acupuncture treatment by using a non-invasive placebo needle [39] with the same acupoints as the treatment group. This placebo needle has been widely used in clinical research on placebo acupuncture treatment of insomnia [19,40-41], and studies have shown that using this needle in a placebo acupuncture group is reliable for the Chinese population [42]. Subjects from both the treatment group and the control group will be treated equally by the physician to prevent them from perceiving the difference.

## 2.4. Outcome measures

### 2.4.1. Primary outcome measures

The primary outcome of this study will be changes in the PSQI and ISI between the baseline, post-treatment assessment, one-week follow-up and one-month follow-up (Table 1).

The PSQI consists of 19 self-evaluation items and 5 other evaluation items. The self-assessment items assess sleep quality, fall asleep time, total sleep time, sleep efficiency, concomitant symptoms, hypnotic drugs, and daytime functions. The total score is 0-21 points. Higher scores indicate worse sleep quality and more severe sleep disorders [22]. The PSQI is widely used in the clinic to assess sleep dysfunction [43], and it is more

likely to assess an individual's sleep state on weekdays [44]. A total score > 5 indicates a need for clinical treatment [45]. The Chinese version of the PSQI has a high degree of reliability and validity for the Chinese population and can be used as an effective tool for sleep screening and evaluation in clinical and scientific research [46-47].

The ISI mainly evaluates the insomnia nature, insomnia severity, and effects of daytime function on patients. The scale is simple and easy to implement. It consists of 7 evaluation items with a total score of 0-28. The higher the score, the more serious the degree of insomnia [24]. It is mainly used for the screening of patients with insomnia and the evaluation of a therapeutic effect in clinical studies [48]. A total score of 8-14 indicates subclinical insomnia, and a total score > 14 indicates clinical insomnia. A change score of −8.4 points is associated with moderate improvement as rated by an independent assessor after treatment in the clinical sample [24, 49]. The Chinese version of the ISI is used in China's population assessment for insomnia with high reliability and validity [50].

**2.4.2. Secondary outcome measures**

The secondary outcome measures consist of (1) changes in the number of awakenings (NOA), total wake time (TWT), total sleep time (TST), and sleep efficiency (SE) measured by actigraphy before and after treatment; (2) changes in BAI, BDI, and FSS scores after treatment and during follow-up compared with before treatment; (3) changes in sleep onset latency (SOL), total wake time (TWT), total sleep time (TST), sleep efficiency (SE), and middle of the night wake after sleep onset (MWASO) from the sleep diary after treatment compared with those before treatment (Table 1).

ACT evaluates the body state by measuring the body movement by wearing a motion sensor on the non-dominant wrist. It can be used as one of the objective indicators for evaluating sleep-wake state [25]. It can satisfactorily evaluate the four sleep indicators: number of awakenings, wake time after sleep onset, total sleep time, and sleep efficiency percentage [51]. Early studies have shown that ACT has a good fit to polysomnography (PSG) in assessing sleep and wakefulness (Rs = 0.52–0.71) and has a good sensitivity as an index of effect evaluation in insomnia treatment [52-53]. The motion watch 8 wrist ACT produced by CamNtech Ltd. will be used in this study. Its

acceleration sensitivity is <0.01 g, with 5 s as the analysis unit. The recorded sleep and activity data will be analysed by the corresponding MotionWare Software. The main parameters include sleep-wake parameters and rest-activity parameters. In this study, we will use ACT combined with a sleep diary [26] to record the sleep of the subjects for one continuous week.

The BAI, which was developed by Beck in 1988 [54], contains a total of 21 different anxiety symptom items. It is used to evaluate the anxiety state of a subject in the past week. The higher the score, the more serious the degree of anxiety. Generally, BAI ≥ 45 is used as the criterion for positive anxiety. This study will exclude subjects with non-primary insomnia. The scale is simple in content, easy in operation, and clear in understanding. The Chinese version has good reliability and validity. It is a commonly used measurement tool for anxiety symptom assessment in the Chinese population [55].

The BDI is based on the diagnostic criteria for depression in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. The first version was published in 1961 and revised to the current version by Beck et al. The scale has a total of 21 items that are used to evaluate the severity of a subject's depression over the past week. The higher the total score is, the more severe the depression. A total score of 0-13 is known as no depression, 14-19 as mild depression, 20-28 as moderate depression and 29-63 as major depression. The Chinese version has been tested and proven to have good reliability and validity [56].

The FSS [29] was formulated by Krupp in 1989. The scale has a total of 9 items and is simple and easy to perform. A higher score indicates more severe fatigue. In insomnia patients, the FSS threshold is 5.5 points, and a high score represents the impaired daytime functional status of insomnia patients [57]. The Chinese version of this scale has been determined to have good reliability and validity [58].

**2.4.3. Safety assessments**

Safety will be assessed by routine blood test, renal function test and liver function test. These indicators are detected during the period of screening and after the treatment. We will still count the events during the trial through a list of adverse events. We will specifically evaluate them during the assessment phase [59] (Table 1). Adverse events

will be defined as any adverse medical reactions that occurred from the time the subject signed the informed consent form to the time of the last follow-up, whether or not there is a causal relationship with the study treatment. Subjects are required to fill in the list of adverse events, which should record the time point, severity, measures taken, whether they are related to the treatment and prognosis. During the assessment phase, researchers will assess the possible relationship between adverse events and the study, as well as the combined medications. Adverse events include all adverse reactions that are definitely related to treatment, most likely related to treatment and likely related to treatment.

| Week | 0 | 1 | 2 | 3 | 4 | 8 |
|---|---|---|---|---|---|---|
| | Baseline | Treatment phase | | | | Follow-up phase |
| PATIENTS | | | | | | |
| Telephone reservation | × | | | | | |
| Enrolment | × | | | | | |
| Sign informed consent | × | | | | | |
| Clinical interview | × | | | | | |
| Sleep scales | × | | | | | |
| Physical examination | × | | | | × | |
| Laboratory test | × | | | | × | |
| PSG | × | | | | | |
| GROUPS | | | | | | |
| Acupuncture group (normal sleep duration) | | Ten treatments | | | | |
| Control group (normal sleep duration) | | Ten treatments | | | | |
| Acupuncture group (short sleep duration) | | Ten treatments | | | | |
| Control group (short sleep duration) | | Ten treatments | | | | |
| OUTCOME MEASUREMENT | | | | | | |
| PSQI | × | | | | × | × |
| ISI | × | | | | × | × |
| ACT | × | | | | × | |
| BAI | × | | | | × | |
| BDI | × | | | | × | |
| FSS | × | | | | × | |
| Sleep diary | × | × | × | × | × | |
| Adverse events | | | | | | |
| Reasons for dropouts or withdrawals | | × | × | × | × | × |
| Patient's compliance | | | | | × | × |

Note:

ACT: Actigraphy

BAI: Beck Anxiety Inventory

BDI: Beck Depression Inventory

FSS: Fatigue Severity Scale

ISI: Insomnia Severity Index

PSG: Polysomnography

PSQI: Pittsburgh Sleep Quality Index

Table 1. Trial processes chart

## 2.5. Sample size

According to previous literature [19], placebo acupuncture reduced the PSQI of chronic insomnia to 14.76 after treatment, and the standard deviation was 3.35. We hypothesize that the true acupuncture in our study could reduce the PSQI score by 2.2 points compared with the placebo acupuncture, and the standard deviation of 2.93 was taken from the previous research results. According to the needs of this study, we made α=0.05 and 1-β=0.90, according to the formula [60]:

$$n = \psi^2\left(\sum S_i^2/g\right)/\left[\sum\left(\overline{X_i} - \overline{X}\right)^2/(g-1)\right]$$

$\overline{X_1}$=12.56, $S_1$=2.93, $\overline{X_2}$=14.76, $S_2$=3.35, $\overline{X_3}$=12.56, $S_3$=2.93, $\overline{X_4}$=14.76, $S_4$=3.35, and $\overline{X}$=13.66; by looking up the table, $\psi$=2.17. Calculating the sample size of each group: n=30.92≈31; considering the loss factor (according to a 20% loss rate), the number of samples in each group is 38 cases, and the total number of samples in the 4 subgroups is 152 cases.

## 2.6. Randomization and blinding

The statistician outside the study will use SPSS 25.0 to generate two different sets of random numbers lists with 76 numbers in each. The random numbers in each list will be arranged in ascending order, with No. 1-38 for the control group and 39-76 for the acupuncture group. Subjects will enter the control group or the acupuncture group according to the random numbers corresponding to the order of signing the informed consent in a ratio of 1:1.

Random numbers and treatment protocols will be printed on the subject's treatment card and placed in an opaque envelope by an independent investigator. Each enrolled subject will be assigned to an order number and receive an envelope with their name on it. The acupuncturist will check whether the envelope was sealed and will open and remove the treatment card. During the trial, the generation of a random numbers list, subjects' recruitment, acupuncture treatment, outcome measures assessment, and follow-up will be performed independently by different researchers. Only the outside assistant and the acupuncturist will be aware of the allocation. Participants and other

relevant researchers will be blinded to the allocation.

### 2.7 Data Collection and Management

Data will be collected at the baseline (one week before the first intervention), post intervention (at the end of intervention), one-week follow-up and one-month follow-up. Each visit will comprise three assessments: (1) subjects will complete sleep-related questionnaires independently in a private conference room at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. Completion of the questionnaires will require approximately 30 min; during this time, outcomes assessors will be available to answer questions; (2) subjects will complete a sleep diary at home under the guidance of outcome assessors; (3) subjects will undergo one-night PSG at the baseline, ACT before and after the intervention. Outcome assessors will be trained to promote participant retention, collect good quality data and complete follow-up. Data analysts will be trained on data entry, coding, security and storage. Statisticians in the research team will provide training on data assessment and analysis. Maintenance of participant confidentiality will be involved: (1) asking subjects only share personal and study-related information during our study; (2) storing data in the password-protected files on a designated specific computer with restricted access; (3) Only the research-related person have access to personal identifiable information, which will be destroyed once the study is completed. Technical appendix, statistical code, and dataset available from the ResMan (www.medresman.org).

### 2.8 Statistics and Analysis

The statistics and analysis of all data will be performed by two analytical researchers independent of the trial. SPSS 25.0 will be used for statistical analysis. For the measurement data that conform to the normal distribution and homogeneous variance, the mean ± standard deviation will be used to describe the discrete tendency and central tendency. The comparison between the two groups will be performed by independent-samples t test. The comparison of multiple time points will be based on repeated

measurement data combined with multivariate analysis of variance. Measurement data that do not conform to the normal distribution will be described by median, minimum, and maximum. The Mann-Whitney U rank sum test will be used for comparison between the two groups. The intra-group comparison will be based on the Friedman(F) rank sum test of the relevant samples.

The enumeration data will be expressed by frequency and constituent ratio. If the analysis index is two-category and multi-category unordered data, the comparison between groups will be performed by $\chi^2$ test. If the analysis index is hierarchical order enumeration data, the Mann-Whitney U rank sum test will be used for the intra-group comparison.

All statistical tests will be performed on a two-sided test, and $P \leq 0.05$ will be considered statistically significant.

## 3. Discussion

Some scholars have suggested that insomnia can be divided into two phenotypes based on objective sleep duration, namely, insomnia with short sleep duration and with normal sleep duration. The former is an important phenotype of insomnia and has more serious health hazards [3-9]. At present, the treatment of insomnia tends to be biologically based (represented by benzodiazepine receptor agonists) and behaviourally based (represented by CBT-I). Most of the diagnosis and treatment guidelines of sleep disorders recommend CBT-I as the primary choice for treatment of insomnia and drug therapy as the secondary choice [11-13]. However, studies have shown that patients with insomnia with a short sleep duration are not sensitive to CBT-I treatment [14], so these patients can only resort to drug therapy. However, drug therapy has many adverse reactions, such as hangover effects, cognitive impairment and drug addiction [15-16]. It is important to seek safe and effective complementary and alternative medicine with few side effects. This is the basis of our research. Acupuncture treatment for insomnia provides such an opportunity.

In this study, our first purpose is to determine whether acupuncture has a therapeutic

effect on insomnia compared with the placebo acupuncture group. Second, we will determine whether acupuncture has a curative effect on insomnia with short sleep duration. Finally, we will examine whether acupuncture treatment for two phenotypes of insomnia has a difference in efficacy.

In fact, past studies have not completely found a reliable method to properly define the insomnia phenotype, which is largely due to the lack of biomarkers for insomnia or objective indicators that can be used for classification. Some clinical practice guidelines do not recommend PSG as a diagnostic tool and a severity assessment tool for insomnia [61]. However, an increasing number of studies have shown that the use of objective sleep assessment tools to classify insomnia has a great effect on the analysis of many potential disease incidences [9-10,62]. This study provides further support for the use of an objective sleep index to help diagnose and treat the specific phenotypes of insomnia.

This study used actigraphy as a sleep time measurement tool and an objective assessment tool for sleep without introducing the PSG. Compared with actigraphy, PSG requires a bed rest time of approximately 8 h, but actigraphy does not have this limitation. By reviewing the previous literature comparing the differences between the two measurement tools [52-53,63-64], actigraphy has a good fit to PSG in assessing the time of sleep and wakefulness in insomnia patients. However, to a certain extent, actigraphy is more likely to underestimate sleep maintenance time and overestimate the total arousal time, which may result in some of the subjects with a total sleep time > 6 h being included in the group of patients with insomnia with short sleep duration. However, first, the gap is small. Second, the conclusions of these differences under this inclusion criterion may represent a greater actual difference between the two phenotypes. In addition, using one-night PSG to evaluate the subject's objective sleep time has a first-night effect. Therefore, we chose a week of actigraphy data to assess the objective indicators. Moreover, previous studies have shown that actigraphy can be used as a useful and efficient tool to assess the sleep patterns of individuals in their own sleep environment [65-66].

This study is the first trial to use acupuncture as an intervention to treat different phenotypes of insomnia. Our conclusions will expand the research results of previous

studies and will further explain that insomnia with short objective sleep duration is a biologically more serious insomnia phenotype. These patients require more specific attention and more specific treatment options.

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## Author Contributions

CW and YFC conceived the research plan. CW and WJY drafted the protocol. XTY, CF, JJL and JD coordinated the study. WLX, YXZ and CW recruited the subjects. CW and WJY formed the analysis plan. All authors participated in, read and approved the final manuscript.

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This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

## Competing interests

None declared.

## Patient consent for publication

Obtained.

## Ethics approval

The trial has been approved by the ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (No.: 2019-17).

## Provenance and peer review

Not commissioned; externally peer reviewed.

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# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 1 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 1 |
| Protocol version | #3 | Date and version identifier | n/a |
| Funding | #4 | Sources and types of financial, material, and other support | 18 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 18 |

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|---|---|---|---|
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | n/a |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | n/a |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |
| **Introduction** | | | |
| 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 | 3 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 3 |
| Objectives | #7 | Specific objectives or hypotheses | 4 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 4 |
| **Methods: Participants, interventions, and outcomes** | | | |
| 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 | 4 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will | 7 |

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|---|---|---|---|
| | | perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | n/a |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | n/a |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | n/a |
| 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 | n/a |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 6 |
| 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 | 13 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 14 |

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| 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 | 14 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 14 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 14 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 14 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 15 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 15 |
| 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 | 15 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 15 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | n/a |

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| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | n/a |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | n/a |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| 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 | 11 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n/a |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 19 |
| 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) | n/a |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | n/a |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 14 |

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| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 18 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | n/a |
| 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 | n/a |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | n/a |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

BMJ Open

# Acupuncture for Insomnia with Short Sleep Duration: Protocol for a Randomized Controlled Trial



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# Acupuncture for Insomnia with Short Sleep Duration: Protocol for a Randomized Controlled Trial

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## Abstract

**Introduction:** Insomnia with short sleep duration has a more serious negative impact on patient health. The existing literature suggests that medication therapy is more effective for this phenotype of insomnia compared to cognitive behavioural therapy (CBT). However, the potential side effects of hypnotic medications hinder their clinical application. Acupuncture has been widely used in the treatment of insomnia, but it remains unclear whether it has therapeutic efficacy for insomnia with short sleep duration. The purpose of this trial is to evaluate the efficacy and safety of acupuncture for insomnia with short sleep duration.

**Methods and analysis:** This study is designed as a randomized, single centre, single-blinded, placebo acupuncture controlled trial involving 152 participants. Eligible patients will be divided into two groups according to the objective total sleep time: insomnia with normal sleep duration group and insomnia with short sleep duration group. Then, patients in each group will be randomly assigned to two subgroups, the treatment group (acupuncture) and the control group (placebo acupuncture), in a 1:1

ratio with 38 subjects in each subgroup. The primary outcome is the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). Secondary outcomes are actigraphy (ACT), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI) and the Fatigue Severity Scale (FSS). All adverse effects will be assessed by the Treatment Emergent Symptom Scale. Outcomes will be evaluated at baseline, post-treatment, as well as at 1-week and 1-month follow-up.

**Ethics and dissemination:** This protocol has been approved by the ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (No.: 2019-17). Written informed consent will be obtained from all participants. The results will be disseminated through peer-reviewed journals for publications.

**Registration:** ChiCTR1900023473; Pre-results.

**Keywords** Acupuncture; Insomnia; Short Sleep Duration; Randomized controlled trial; Protocol.

## Article Summary

## Strengths and limitations of this study

1. A randomized, single centre, placebo acupuncture controlled trial with a 2×2 factorial design.
2. The first trial to study the efficacy and safety of acupuncture for insomnia with short sleep duration.
3. Participants will be screened for insomnia at baseline by polysomnography (PSG).
4. Sleep indicators in the actigraphy (ACT) will be used as objective outcomes of patients' sleep quality.
5. One limitation is that this study is implemented in only one center in Chinese subjects and without long-term treatment and follow-up.

# 1. Introduction

In recent years, the incidence of chronic insomnia in adults has become higher [1], and short sleepers are also showing an increasing trend [2]. Studies have found that patients with insomnia accompanied by short sleep duration can cause many chronic diseases, such as obesity, diabetes, cardiovascular disease, chronic kidney disease, and hypertension [3-7], and may even result in inadequate hydration [8]. Similarly, insomnia patients with short sleep duration will have many adverse effects on their health. Some researchers have found that the mortality rate of insomnia patients is three times more than that of people without insomnia. When patients with insomnia have short sleep duration, the damage to their health will be more serious and the mortality rate will be higher [9].

Based on this, Vgontzas [10] proposed that insomnia can be divided into two phenotypes based on objective sleep duration, with the threshold of the total sleep time being 6 h. The first phenotype (short objective sleep duration) is characterized by physiological hyperarousal with numerous medical complications. The second phenotype (normal sleep duration) is characterized by cognitive-emotional disorders, accompanied by a process of cortical excitement and remitting course. Vgontzas also suggested that insomnia with short sleep duration may be less sensitive to CBT-I therapy. Although many guidelines of sleep disorders recommend CBT-I as the primary treatment [11-13], Bathgate et al conducted a trial and concluded that insomnia with short sleep duration has a dull response to CBT-I therapy [14]. The short objective sleep duration phenotype (characterized by physiological hyperarousal) has a dull response to CBT-I because of behaviourally based approach aimed at decreasing cognitive–emotional arousal, altering unhealthy sleep-related behaviours and beliefs and changing sleep misperceptions [15]. It's different from the pathological mechanism of this phenotype. But it will respond better to biologically based treatments, since selected medications aim to reduce physiological hyperarousal and increase sleep duration [16].

Because insomnia with short sleep duration has a dull response to CBT-I treatment, these patients prefer to take sleep medicine. However, there are many side effects to

benzodiazepine receptor agonists, such as hangover effects, cognitive impairment, and drug addiction [17-18]. Therefore, many people with insomnia seek complementary and alternative medicine, such as acupuncture [19]. Acupuncture has been widely used in the treatment of insomnia, and studies have shown that it can improve sleep efficiency, daytime functioning, psychological health and sleep quality of insomnia subjects [20-21]. Our previous research also showed that acupuncture has a good short-term effect on perimenopausal insomnia [22]. An earlier Cochrane review showed that acupuncture can improve the sleep quality of insomnia subjects compared with untreated groups and placebo acupuncture groups [23].

According to the theory of TCM, the main causes of insomnia are Yin deficiency leading to excessive fire, incoordination between the heart and the kidney, disturbance of heart due to phlegm heat and so on [24]. Therefore, we chose acupoints based on disease differentiation and special acupoints combinations to nourish Yin and drain fire, calm the mind and regulate mentality. SP 6 (Sanyinjiao) and HT 7 (Shenmen) are adopted as the main points to nourish Yin and drain fire, especially used to nourish liver and kidney Yin and decrease heart fire [25]. PC 6 (Neiguan) is the collateral point of the hand-jueyin pericardium meridian, which is also specific acupuncture point of the eight confluent points. It's used to cool pericardium and restore consciousness [26]. We also use GV20 (Baihui) and Ex-HN 1 (Sishencong) to make the brain-activating and mind-tranquilizing [27].

This is the first rigorous randomized controlled clinical trial to study the therapeutic effect of acupuncture on insomnia with short sleep duration and compare the effects on different insomnia phenotypes. Our objectives are as follows: (1) In randomized controlled trials with a 2×2 factorial design, we will study whether the clinical effect of acupuncture on chronic insomnia is related to insomnia phenotypes or acupoint effects and will evaluate both subjective and objective parameters. (2) We will explore the clinical symptomatic manifestations (difficulty in falling asleep, early awakening, difficulty in maintaining sleep, etc.) and psychological characteristics (anxiety, depression, sensitivity, etc.) and analyse the acupuncture effect for these symptoms of insomnia with short sleep duration.

# 2. Methods

## 2.1. Study design

This study is a randomized controlled trial with a single-centre, single-blind, 2×2 factorial design and will be completed in Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. The study period will be from November 2019 to April 2021, and the Shanghai Municipal Commission of Health and Family Planning will be the management organization of the study.

Insomnia subjects who meet the inclusion criteria will be divided into two groups according to the objective total sleep time (TST): insomnia with a short sleep duration group (objective sleep time < 6 h) and insomnia with a normal sleep duration group (objective sleep time ≥ 6 h). A total of 76 subjects will be recruited from each group. Each group will be randomly assigned to the acupuncture subgroup and the placebo acupuncture subgroup at a 1:1 ratio. The aim of this study is to evaluate the short-term efficacy of acupuncture for the treatment of insomnia with short sleep duration. According to our previous research, each subject will experience screening, treatment and a follow-up period of approximately 8 weeks.

All subjects will complete the following scales [28]: The Pittsburgh Sleep Quality Index (PSQI) [29] and the Insomnia Severity Index (ISI) [30-31] will evaluate subjects' subjective sleep improvement. Subjects will be assessed for the objective total sleep time by actigraphy [32] in conjunction with a sleep diary [33]. Subjects' mood improvement will be evaluated by the Beck Anxiety Inventory (BAI) [34] and the Beck Depression Inventory (BDI) [35]. The Fatigue Severity Scale (FSS) [36] will be used to assess the improvement in fatigue. The above scales or actigraphy will be evaluated during the screening period and after the treatment at one-week and one-month follow-ups (Figure 1). PSG (NIHON KOHDEN, Japan) in this study will be used for screening purposes only. Subjects will sign the informed consent form after enrolment.

## 2.2. Participants

The study will include 152 insomnia participants. We plan to recruit participants in multiple ways, and the recruitment location will be restricted to Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine, Shanghai, China. Our hospital is a comprehensive tertiary hospital with clinical treatment, scientific research and teaching practice. The main source of the subjects will be the outpatients who meet our criteria. In addition, we will also recruit participants through newspapers, social media and advertising. The time limit will be from November 2019 to April 2021. The site of our clinical trial will be the Insomnia Diagnosis and Treatment Center of the Acupuncture and Moxibustion Department at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. All participants who are willing to participate in the trial will be required to call our research coordinator and arrange an outpatient interview on the first available date.

### 2.2.1. Inclusion criteria

The outpatient interview will be conducted in the form of a semi-structured interview questionnaire, which will contain the cause of insomnia, onset process, treatment process, main sleep complaints, bedtime status, sleep-wake cycle, other sleep-related symptoms, daytime symptoms, mental state, etc. [37]. The inclusion criteria have been developed based on the diagnostic criteria for chronic insomnia in the International Classification of Sleep Disorders (Third Edition) (ICSD-3) [38] developed by the American Academy of Sleep Medicine in 2014. The inclusion criteria are as follows:

(1) Between 18 and 65 years of age;

(2) Compliance with the diagnostic criteria for chronic insomnia in ICSD-3;

(3) Stable administration of sedative-hypnotic drugs for more than 3 months before entering the study or not taking such drugs;

(4) Meet all of the following: PSQI [29] > 5 points, ISI [30-31] > 14 points, BAI [34] < 45 points and BDI [35] ≤ 28 points;

(5) Never received acupuncture treatment;

(6) Voluntarily participated in the study and signed informed consent.

In addition, all participants will complete a one-week sleep actigraphy and diary to determine their sleep patterns and objective sleep duration before enrolment [39]. We will recruit 76 subjects in each group (insomnia with short sleep duration and insomnia with normal sleep duration). If one group completes recruitment first, that specific group will stop recruiting.

**2.2.2. Exclusion criteria**

The exclusion criteria are as follows:

(1) Severe hepatic and renal function damage, as well as haematologic diseases and respiratory diseases and diagnosis of mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [40];

(2) Semi-structured clinical interviews determine subjects have other sleep disorders rather than primary insomnia;

(3) Infectious diseases such as infectious hepatitis, tuberculosis, AIDS, and syphilis;

(4) Severe digestive system diseases and severe malnutrition;

(5) Pregnant or lactating;

(6) Severe trauma with no cure or not suitable for acupuncture, such as allergic constitution and severe dermatosis;

(7) An apnoea–hypopnea index (AHI) >10 or periodic limb movements index during sleep associated with >15 arousals per hour on diagnostic PSG [41];

(8) Participated in other clinical trials in the last 3 months.

## 2.3. Interventions

The acupuncturist for this study has received a master's degree in acupuncture and tuina at Shanghai University of Traditional Chinese Medicine, has 8 years of training experience, has obtained a doctor qualification certificate, and has 3 years of clinical work experience. All study participants will receive 10 days of training prior to the start of the trial to become more familiar with the process.

The subjects in the acupuncture group will be placed in the supine position. We have selected 5 acupoints for this study: GV20 (Baihui), PC 6 (Neiguan), SP 6 (Sanyinjiao),

HT 7 (Shenmen) and Ex-HN 1 (Sishencong). The reason for choosing these acupoints is the previous systematic review [42-43] and our clinical experience. A disposable sterile stainless steel acupuncture needle with a length of 40 mm and a diameter of 0.25 mm will be used (Andy, Guizhou, China). The acupuncturist will take the points on both sides of the body. The needle will be inserted into the skin to a depth of 10-20 mm, which is determined by the acupuncturist according to body type (high or short, fat or thin). After piercing, a thrusting and twirling of the needle will be performed to induce the sensation of "De qi", and the needle will be left for 20 minutes [44]. "De qi" means that after the needle has penetrated into the acupoint to a certain depth, the needle is thrust and twirled to cause the acupoint to obtain the induction of meridian qi. The subjects will have a self-conscious reaction such as soreness, heaviness or distention. This is the key process in acupuncture treatment [45].

Subjects who entered the control group will receive a placebo acupuncture treatment by using a non-invasive placebo needle [46] with the same acupoints as the treatment group. The Streitberger needle has been widely used in clinical research on placebo acupuncture treatment of insomnia [22,47-48], and studies have shown that using this needle in a placebo acupuncture group is reliable for the Chinese population [49]. Since the Streitberger needles will be in place for 20min, they will need to be firmly affixed to the skin or scalp. We have modified the procedure by using surgical tape (or hairpins in hairy regions) to hold the needles in place. This enables the needles to be applied in hairy regions and different needling directions to be attempted. Such a method has been adopted by mang other researchers [50].

Subjects from both the treatment group and the control group will be treated equally by the physician to prevent them from perceiving the difference. They will be informed about the acupuncture as follows: "In this study, different types of acupuncture treatment will be compared. One type is the usual acupuncture, and the other is associated with positive outcomes in previous clinical studies [51]." And subjects in both groups will be treated three times per week for 10 times by the same acupuncturist.

## 2.4. Outcome measures

### 2.4.1. Primary outcome measures

Because PSQI and ISI can evaluate global sleep and insomnia symptoms, many guidelines recommend both as an essential indicator for measuring and reporting about insomnia symptoms [28] [52]. And PSQI was verified as a reliable and valid measure of subjective sleep quality in clinical practice and experimental research [53-54]. At the same time, combined with our previous research results, the primary outcome of this study will be the changes in the PSQI and ISI between the baseline, post-treatment assessment, one-week follow-up and one-month follow-up (Table 1). And PSQI will be used for sample size calculations.

The PSQI consists of 19 self-evaluation items and 5 other evaluation items. The self-assessment items assess sleep quality, fall asleep time, total sleep time, sleep efficiency, concomitant symptoms, hypnotic drugs, and daytime functions. The total score is 0-21 points. Higher scores indicate worse sleep quality and more severe sleep disorders [29]. The PSQI is widely used in the clinic to assess sleep dysfunction [55], and it is more likely to assess an individual's sleep state on weekdays [56]. A total score > 5 indicates a need for clinical treatment [57]. The Chinese version of the PSQI has a high degree of reliability and validity for the Chinese population and can be used as an effective tool for sleep screening and evaluation in clinical and scientific research [58-59].

The ISI mainly evaluates the insomnia nature, insomnia severity, and effects of daytime function on patients. The scale is simple and easy to implement. It consists of 7 evaluation items with a total score of 0-28. The higher the score, the more serious the degree of insomnia [31]. It is mainly used for the screening of patients with insomnia and the evaluation of a therapeutic effect in clinical studies [60]. A total score of 8-14 indicates subclinical insomnia, and a total score > 14 indicates clinical insomnia. A change score of −8.4 points is associated with moderate improvement as rated by an independent assessor after treatment in the clinical sample [31, 61]. The Chinese version of the ISI is used in China's population assessment for insomnia with high reliability and validity [62].

### 2.4.2. Secondary outcome measures

The secondary outcome measures consist of (1) changes in the number of awakenings (NOA), total wake time (TWT), total sleep time (TST), and sleep efficiency (SE) measured by actigraphy before and after treatment; (2) changes in BAI, BDI, and FSS scores after treatment and during follow-up compared with before treatment; (3) changes in sleep onset latency (SOL), total wake time (TWT), total sleep time (TST), sleep efficiency (SE), and middle of the night wake after sleep onset (MWASO) from the sleep diary after treatment compared with those before treatment (Table 1).

ACT evaluates the body state by measuring the body movement by wearing a motion sensor on the non-dominant wrist. It can be used as one of the objective indicators for evaluating sleep-wake state [32]. The motion watch 8 wrist ACT produced by CamNtech Ltd will be used in this study. Its acceleration sensitivity is <0.01 g, with 5 s as the analysis unit. The recorded sleep and activity data will be analysed by the corresponding MotionWare Software. The main parameters include sleep-wake parameters and rest-activity parameters. It can satisfactorily evaluate the four sleep indicators: number of awakenings, wake time after sleep onset, total sleep time, and sleep efficiency percentage [63]. Early studies have shown that ACT has a good fit to polysomnography (PSG) in assessing sleep and wakefulness (Rs = 0.52–0.71) and has a good sensitivity as an index of effect evaluation in insomnia treatment [64-65]. In this study, we will use ACT combined with a sleep diary [33] to record the sleep of the subjects for one continuous week. Changes in the number of awakenings (NOA), total wake time (TWT), total sleep time (TST), and sleep efficiency (SE) will be measured before and after treatment.

The BAI, which was developed by Beck in 1988 [66], contains a total of 21 different anxiety symptom items. It is used to evaluate the anxiety state of a subject in the past week. The higher the score, the more serious the degree of anxiety. Generally, BAI ≥ 45 is used as the criterion for positive anxiety. The scale is simple in content, easy in operation, and clear in understanding. The Chinese version has good reliability and validity. It is a commonly used measurement tool for anxiety symptom assessment in the Chinese population [67].

The BDI is based on the diagnostic criteria for depression in the fourth edition of the

Diagnostic and Statistical Manual of Mental Disorders. The first version was published in 1961 and revised to the current version by Beck et al. The scale has a total of 21 items that are used to evaluate the severity of a subject's depression over the past week. The higher the total score is, the more severe the depression. A total score of 0-13 is known as no depression, 14-19 as mild depression, 20-28 as moderate depression and 29-63 as major depression. The Chinese version has been tested and proven to have good reliability and validity [68].

The FSS [36] was formulated by Krupp in 1989. The scale has a total of 9 items and is simple and easy to perform. A higher score indicates more severe fatigue. In insomnia patients, the FSS threshold is 5.5 points, and a high score represents the impaired daytime functional status of insomnia patients [69]. The Chinese version of this scale has been determined to have good reliability and validity [70].

**2.4.3. Safety assessments**

Safety will be assessed by routine blood test, renal function test and liver function test. These indicators are detected during the period of screening and after the treatment. We will still count the events during the trial through a list of adverse events. We will specifically evaluate them during the assessment phase [71] (Table 1). Adverse events will be defined as any adverse medical reactions that occurred from the time the subject signed the informed consent form to the time of the last follow-up, whether or not there is a causal relationship with the study treatment. Subjects are required to fill in the list of adverse events, which should record the time point, severity, measures taken, whether they are related to the treatment and prognosis. During the assessment phase, researchers will assess the possible relationship between adverse events and the study, as well as the combined medications. Adverse events include all adverse reactions that are definitely related to treatment, most likely related to treatment and likely related to treatment.

| Week | 0 | 1 | 2 | 3 | 4 | 8 |
|---|---|---|---|---|---|---|
| | Baseline | Treatment phase | | | | Follow-up phase |
| PATIENTS | | | | | | |
| Telephone reservation | × | | | | | |
| Enrolment | × | | | | | |
| Sign informed consent | × | | | | | |
| Clinical interview | × | | | | | |
| Sleep scales | × | | | | | |
| Physical examination | × | | | | × | |
| Laboratory test | × | | | | × | |
| PSG | × | | | | | |
| GROUPS | | | | | | |
| Acupuncture group (normal sleep duration) | | Ten treatments | | | | |
| Control group (normal sleep duration) | | Ten treatments | | | | |
| Acupuncture group (short sleep duration) | | Ten treatments | | | | |
| Control group (short sleep duration) | | Ten treatments | | | | |
| OUTCOME MEASUREMENT | | | | | | |
| PSQI | × | | | | × | × |
| ISI | × | | | | × | × |
| ACT | × | | | | × | |
| BAI | × | | | | × | |
| BDI | × | | | | × | |
| FSS | × | | | | × | |
| Sleep diary | × | × | × | × | × | |
| Success of subject-blinding test | | | | | × | |
| Adverse events | | | | | | |
| Reasons for dropouts or withdrawals | | × | × | × | × | × |
| Patient's compliance | | | | | × | × |

Note:

ACT: Actigraphy

BAI: Beck Anxiety Inventory

BDI: Beck Depression Inventory

FSS: Fatigue Severity Scale

ISI: Insomnia Severity Index

PSG: Polysomnography

PSQI: Pittsburgh Sleep Quality Index

Table 1. Trial processes chart

## 2.5. Sample size

According to previous literature [22], placebo acupuncture reduced the PSQI of chronic insomnia to 14.76 after treatment, and the standard deviation was 3.35. We hypothesize that the true acupuncture in our study could reduce the PSQI score by 2.2 points compared with the placebo acupuncture, and the standard deviation of 2.93 was taken from the previous research results. According to the needs of this study, we made α=0.05 and 1-β=0.90, according to the formula [72]:

$$n = \psi^2(\sum S_i^2/g)/[\sum(\overline{X_i} - \overline{X})^2/(g-1)]$$

$\overline{X_1}$=12.56, $S_1$=2.93, $\overline{X_2}$=14.76, $S_2$=3.35, $\overline{X_3}$=12.56, $S_3$=2.93, $\overline{X_4}$=14.76, $S_4$=3.35, and $\overline{X}$=13.66; by looking up the table, $\psi$=2.17. Calculating the sample size of each group: n=30.92≈31; considering the loss factor (according to a 20% loss rate), the number of samples in each group is 38 cases, and the total number of samples in the 4 subgroups is 152 cases.

## 2.6. Randomization and blinding

The statistician outside the study will use SPSS 25.0 to generate two different sets of random numbers lists with 76 numbers in each. The random numbers in each list will be arranged in ascending order, with No. 1-38 for the control group and 39-76 for the acupuncture group. Subjects will enter the control group or the acupuncture group according to the random numbers corresponding to the order of signing the informed consent in a ratio of 1:1.

Random numbers and treatment protocols will be printed on the subject's treatment card and placed in an opaque envelope by an independent investigator. Each enrolled subject will be assigned to an order number and receive an envelope with their name on it. The acupuncturist will check whether the envelope was sealed and will open and remove the treatment card. During the trial, the generation of a random numbers list, subjects' recruitment, acupuncture treatment, outcome measures assessment, and follow-up will be performed independently by different researchers. Only the outside assistant and the acupuncturist will be aware of the allocation. Participants and other

relevant researchers will be blinded to the allocation.

The success of subject-blinding will be assessed by, at the end of the last treatment session, asking the subject if they believe they are receiving active treatment.

### 2.7 Data Collection and Management

Data will be collected at the baseline (one week before the first intervention), post intervention (at the end of intervention), one-week follow-up and one-month follow-up. Each visit will comprise three assessments: (1) subjects will complete sleep-related questionnaires independently in a private conference room at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. Completion of the questionnaires will require approximately 30 min; during this time, outcomes assessors will be available to answer questions; (2) subjects will complete a sleep diary at home under the guidance of outcome assessors; (3) subjects will undergo one-night PSG at the baseline, ACT before and after the intervention. Outcome assessors will be trained to promote participant retention, collect good quality data and complete follow-up. Data analysts will be trained on data entry, coding, security and storage. Statisticians in the research team will provide training on data assessment and analysis. Maintenance of participant confidentiality will be involved: (1) asking subjects only share personal and study-related information during our study; (2) storing data in the password-protected files on a designated specific computer with restricted access; (3) only the research-related person have access to personal identifiable information, which will be destroyed once the study is completed. Technical appendix, statistical code, and dataset available from the ResMan (www.medresman.org).

Subjects may withdraw from the study at any time for any reason. If any subject wishes to withdraw, the clinician will ask if they are willing to complete the final assessment and record the time of the last treatment. The incidence of withdrawal and loss to follow-up will be recorded and reported. We will also inquire the subjects about the reasons for absence, and will record compliance by the clinician.

### 2.8 Statistics and Analysis

The statistics and analysis of all data will be performed by two analytical researchers independent of the trial. Intention-to-treat (ITT) and per-protocol (PP) analysis will be used as evaluation methods to evaluate the final results of this study. Among them, ITT analysis will be used as the main analytical method. The multiple imputation method will be the primary method for processing the missing data, and an observation carried forward method will also apply to sensitivity analysis [73]. Data from dropout cases will be managed by both ITT analysis and PP analysis.

SPSS 25.0 will be used for statistical analysis. For the measurement data that conform to the normal distribution and homogeneous variance, the mean ± standard deviation will be used to describe the discrete tendency and central tendency. The comparison between the two groups will be performed by independent-samples t test. The comparison of multiple time points will be based on repeated measurement data combined with multivariate analysis of variance. Measurement data that do not conform to the normal distribution will be described by median, minimum, and maximum. The Mann-Whitney U rank sum test will be used for comparison between the two groups. The intra-group comparison will be based on the Friedman(F) rank sum test of the relevant samples.

The enumeration data will be expressed by frequency and constituent ratio. If the analysis index is two-category and multi-category unordered data, the comparison between groups will be performed by $\chi^2$ test. If the analysis index is hierarchical order enumeration data, the Mann-Whitney U rank sum test will be used for the intra-group comparison.

All statistical tests will be performed on a two-sided test, and $P \leq 0.05$ will be considered statistically significant.

## 3. Discussion

Some scholars have suggested that insomnia can be divided into two phenotypes

based on objective sleep duration, namely, insomnia with short sleep duration and with normal sleep duration. The former is an important phenotype of insomnia and has more serious health hazards [3-9]. At present, the treatment of insomnia tends to be biologically based (represented by benzodiazepine receptor agonists) and behaviourally based (represented by CBT-I). Most of the diagnosis and treatment guidelines of sleep disorders recommend CBT-I as the primary choice for treatment of insomnia and drug therapy as the secondary choice [11-13]. However, studies have shown that patients with insomnia with a short sleep duration are not sensitive to CBT-I treatment [14], these patients prefer to take sleep medicine. However, drug therapy has many adverse reactions, such as hangover effects, cognitive impairment and drug addiction [17-18]. It is important to seek safe and effective complementary and alternative medicine with few side effects. This is the basis of our research. Acupuncture treatment for insomnia provides such an opportunity.

In this study, our first purpose is to determine whether acupuncture has a therapeutic effect on insomnia compared with the placebo acupuncture group. Second, we will determine whether acupuncture has a curative effect on insomnia with short sleep duration. Finally, we will examine whether acupuncture treatment for two phenotypes of insomnia has a difference in efficacy.

In fact, past studies have not completely found a reliable method to properly define the insomnia phenotype, which is largely due to the lack of biomarkers for insomnia or objective indicators that can be used for classification. Some clinical practice guidelines do not recommend PSG as a diagnostic tool and a severity assessment tool for insomnia [74]. However, an increasing number of studies have shown that the use of objective sleep assessment tools to classify insomnia has a great effect on the analysis of many potential disease incidences [9-10,75]. This study provides further support for the use of an objective sleep index to help diagnose and treat the specific phenotypes of insomnia.

This study used actigraphy as a sleep time measurement tool and an objective assessment tool for sleep without introducing the PSG. Compared with actigraphy, PSG requires a bed rest time of approximately 8 h, but actigraphy does not have this limitation. By reviewing the previous literature comparing the differences between the

two measurement tools [64-65,76-77], actigraphy has a good fit to PSG in assessing the time of sleep and wakefulness in insomnia patients. However, to a certain extent, actigraphy is more likely to underestimate sleep maintenance time and overestimate the total arousal time, which may result in some of the subjects with a total sleep time > 6 h being included in the group of patients with insomnia with short sleep duration. However, first, the gap is small. Second, the conclusions of these differences under this inclusion criterion may represent a greater actual difference between the two phenotypes. In addition, using one-night PSG to evaluate the subject's objective sleep time has a first-night effect. Therefore, we chose a week of actigraphy data to assess the objective indicators. Moreover, previous studies have shown that actigraphy can be used as a useful and efficient tool to assess the sleep patterns of individuals in their own sleep environment [78-79].

The use of placebo control in acupuncture trials remains controversial [80]. In pharmacological treatment trials, an ideal placebo should be indistinguishable from the true interventions and be physiologically inert [81]. However, it remains a challenge to design an adequate placebo for non-pharmacological interventions, such as acupuncture, in which non-specific treatment will be exists in the placebo group [82]. Since placebo acupuncture can produce a significant non-specific therapeutic effects, there is little space left for the assumed specific effect of acupuncture [83]. Therefore, we expect that in the future research work, researchers will invent a more authoritative placebo acupuncture.

This study is the first trial to use acupuncture as an intervention to treat different phenotypes of insomnia. Our conclusions will expand the research results of previous studies and will further explain that insomnia with short objective sleep duration is a biologically more serious insomnia phenotype. These patients require more specific attention and more specific treatment options.

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## Author Contributions

CW and YFC conceived the research plan. CW and WJY drafted the protocol. XTY, CF, JJL and JW coordinated the study. WLX, YXZ and CW recruited the subjects. CW and WJY formed the analysis plan. All authors participated in, read and approved the final manuscript.

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## Competing interests

None declared.

## Patient and public involvement

Patients' priorities, experience and preferences were not involved in development of the research question and outcome measures, the design of this study, or the recruitment to and conduct of the study. The results will be not disseminated to study participants.

## Ethics approval

The trial has been approved by the ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (No.: 2019-17).

## Provenance and peer review

Not commissioned; externally peer reviewed.



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**Fig.1. Trial flow chart**

HCG: Human chorionic gonadotropin

PSG: Polysomnography

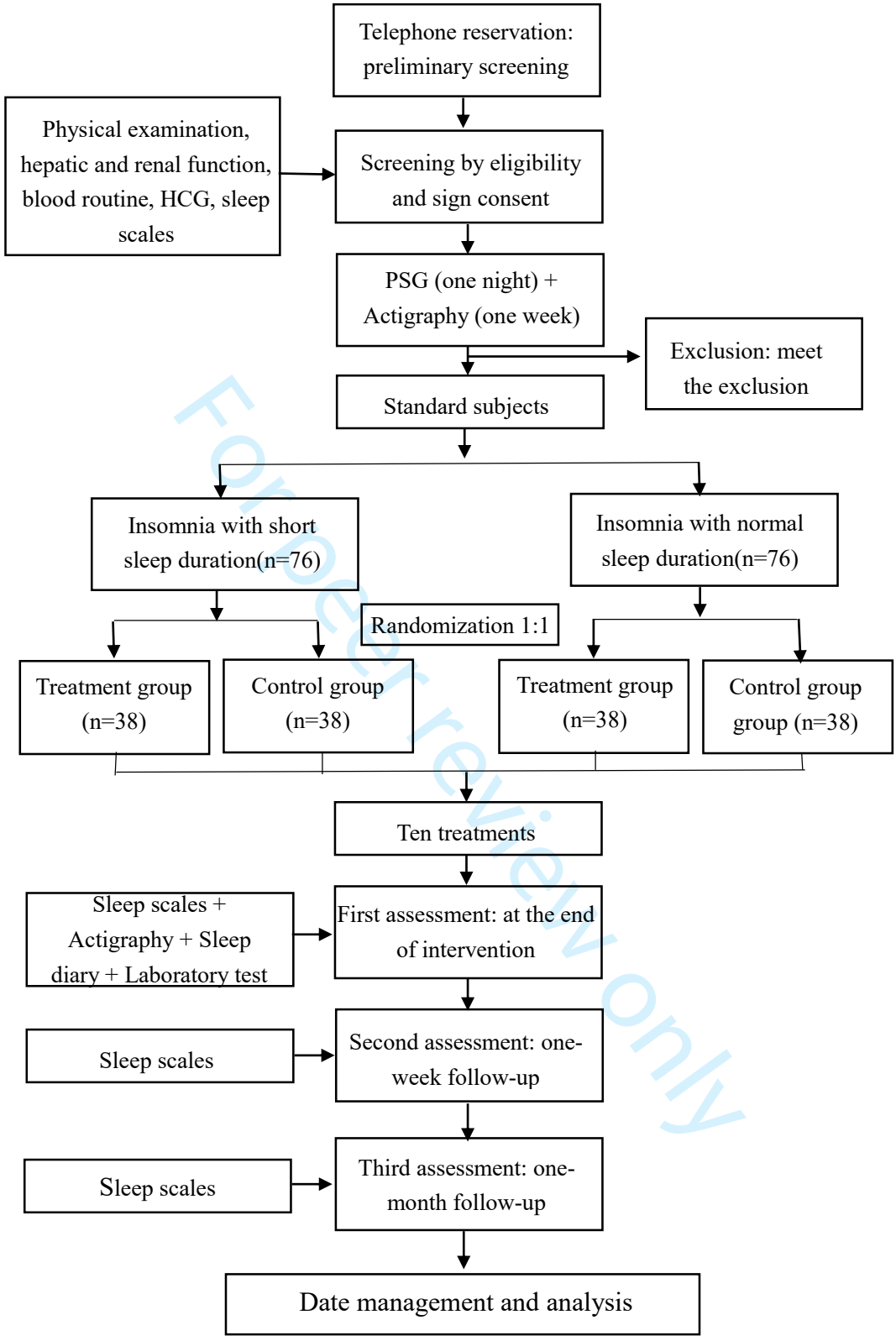


Fig.1. Trial flow chart

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 1 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 1 |
| Protocol version | #3 | Date and version identifier | n/a |
| Funding | #4 | Sources and types of financial, material, and other support | 18 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 18 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | n/a |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | n/a |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |
| **Introduction** | | | |
| 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 | 3 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 3 |
| Objectives | #7 | Specific objectives or hypotheses | 4 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 4 |
| **Methods: Participants, interventions, and outcomes** | | | |
| 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 | 4 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will | 7 |

| | | | |
|---|---|---|---|
| | | perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | n/a |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | n/a |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | n/a |
| 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 | n/a |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 6 |
| 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 | 13 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 14 |

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| 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 | 14 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 14 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 14 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 14 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 15 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 15 |
| 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 | 15 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 15 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | n/a |

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|---|---|---|---|
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | n/a |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | n/a |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| 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 | 11 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n/a |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 19 |
| 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) | n/a |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | n/a |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 14 |

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|---|---|---|---|
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 18 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | n/a |
| 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 | n/a |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | n/a |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

BMJ Open

# Acupuncture for Insomnia with Short Sleep Duration: Protocol for a Randomized Controlled Trial



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# Acupuncture for Insomnia with Short Sleep Duration: Protocol for a Randomized Controlled Trial

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## Abstract

**Introduction:** Insomnia with short sleep duration has a more serious negative impact on patient health. The existing literature suggests that medication therapy is more effective for this phenotype of insomnia compared to cognitive behavioural therapy (CBT). However, the potential side effects of hypnotic medications hinder their clinical application. Acupuncture has been widely used in the treatment of insomnia, but it remains unclear whether it has therapeutic efficacy for insomnia with short sleep duration. The purpose of this trial is to evaluate the efficacy and safety of acupuncture for insomnia with short sleep duration.

**Methods and analysis:** This study is designed as a randomized, single centre, single-blinded, placebo acupuncture controlled trial involving 152 participants. Eligible patients will be divided into two groups according to the objective total sleep time: insomnia with normal sleep duration group and insomnia with short sleep duration group. Then, patients in each group will be randomly assigned to two subgroups, the treatment group (acupuncture) and the control group (placebo acupuncture), in a 1:1

ratio with 38 subjects in each subgroup. The primary outcome is the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI). Secondary outcomes are actigraphy (ACT), the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI) and the Fatigue Severity Scale (FSS). All adverse effects will be assessed by the Treatment Emergent Symptom Scale. Outcomes will be evaluated at baseline, post-treatment, as well as at 1-week and 1-month follow-up.

**Ethics and dissemination:** This protocol has been approved by the ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (No.: 2019-17). Written informed consent will be obtained from all participants. The results will be disseminated through peer-reviewed journals for publications.

**Registration:** ChiCTR1900023473; Pre-results.

**Keywords** Acupuncture; Insomnia; Short Sleep Duration; Randomized controlled trial; Protocol.

## Article Summary

## Strengths and limitations of this study

1. A randomized, single centre, placebo acupuncture controlled trial with a 2×2 factorial design.
2. The first trial to study the efficacy and safety of acupuncture for insomnia with short sleep duration.
3. Participants will be screened for insomnia at baseline by polysomnography (PSG).
4. Sleep indicators in the actigraphy (ACT) will be used as objective outcomes of patients' sleep quality.
5. One limitation is that this study is implemented in only one center in Chinese subjects and without long-term treatment and follow-up.

# 1. Introduction

In recent years, the incidence of chronic insomnia in adults has become higher [1], and short sleepers are also showing an increasing trend [2]. Studies have found that patients with insomnia accompanied by short sleep duration can cause many chronic diseases, such as obesity, diabetes, cardiovascular disease, chronic kidney disease, and hypertension [3-7], and may even result in inadequate hydration [8]. Similarly, insomnia patients with short sleep duration will have many adverse effects on their health. Some researchers have found that the mortality rate of insomnia patients is three times more than that of people without insomnia. When patients with insomnia have short sleep duration, the damage to their health will be more serious and the mortality rate will be higher [9].

Based on this, Vgontzas [10] proposed that insomnia can be divided into two phenotypes based on objective sleep duration, with the threshold of the total sleep time being 6 h. The first phenotype (short objective sleep duration) is characterized by physiological hyperarousal with numerous medical complications. The second phenotype (normal sleep duration) is characterized by cognitive-emotional disorders, accompanied by a process of cortical excitement and remitting course. Vgontzas also suggested that insomnia with short sleep duration may be less sensitive to CBT-I therapy. Although many guidelines of sleep disorders recommend CBT-I as the primary treatment [11-13], Bathgate et al conducted a trial and concluded that insomnia with short sleep duration has a dull response to CBT-I therapy [14]. The short objective sleep duration phenotype has a dull response to CBT-I because of behaviourally based approach aimed at decreasing cognitive–emotional arousal, altering unhealthy sleep-related behaviours and beliefs and changing sleep misperceptions [15]. However, the short objective sleep duration phenotype is mainly associated with cortical, and physiological hyperarousal (i.e., short sleep duration and activation of the stress system), and non-remitting course [10]. Obviously, CBT-I does not completely solve the symptoms of this phenotype. But it will respond better to treatmentsthat primarily aim at decreasing physiological hyperarousal (e.g.,cortisol) and increasing sleep duration,

such as medication or other biological treatments [16].

Because insomnia with short sleep duration has a dull response to CBT-I treatment, these patients prefer to take sleep medicine. However, there are many side effects to benzodiazepine receptor agonists, such as hangover effects, cognitive impairment, and drug addiction [17-18]. Therefore, many people with insomnia seek complementary and alternative medicine, such as acupuncture, especially in China [19]. Acupuncture has been widely used in the treatment of insomnia, and studies have shown that it can improve sleep efficiency, daytime functioning, psychological health and sleep quality of insomnia subjects [20-21]. Our previous research also showed that acupuncture has a good short-term effect on perimenopausal insomnia [22]. An earlier Cochrane review showed that acupuncture can improve the sleep quality of insomnia subjects compared with untreated groups and placebo acupuncture groups [23].

We hypothesized that individuals with insomnia and short sleep duration, would have a better treatment response to acupuncture than individuals with insomnia and normal sleep duration. We made this prediction because some studies have found that insomnia with objective short sleep duration is associated with activation of the stress system, especially the activation of the HPA axis, and the group with an objective short sleep duration had a higher amount of cortisol (COR) compared to the group with normal sleep duration [16] [24-25]. Previous studies about acupuncture have shown that acupuncture can regulate the activity of the HPA axis and reduce adrenocorticotropic hormone (ACTH), corticotrophin releasing hormone (CRH) and COR levels in peripheral blood [26-27].

According to the theory of TCM, the main causes of insomnia are Yin deficiency leading to excessive fire, incoordination between the heart and the kidney, disturbance of heart due to phlegm heat, deficiency of both heart and spleen and liver depression forming fire [28]. Therefore, we chose acupoints based on disease differentiation and special acupoints combinations to nourish Yin and drain fire, calm the mind and regulate mentality. SP 6 (Sanyinjiao) and HT 7 (Shenmen) are adopted as the main points to nourish Yin and drain fire, especially used to nourish liver and kidney Yin and decrease heart fire [29]. PC 6 (Neiguan) is the collateral point of the hand-jueyin

pericardium meridian, which is also specific acupuncture point of the eight confluent points. It's used to cool pericardium and restore consciousness [30]. We also use GV20 (Baihui) and Ex-HN 1 (Sishencong) to make the brain-activating and mind-tranquilizing [31].

This is the first rigorous randomized controlled clinical trial to study the therapeutic effect of acupuncture on insomnia with short sleep duration and compare the effects on different insomnia phenotypes. Our objectives are as follows: (1) In randomized controlled trials with a 2×2 factorial design, we will study whether the clinical effect of acupuncture on chronic insomnia is related to insomnia phenotypes or acupoint effects and will evaluate both subjective and objective parameters. (2) We will explore the clinical symptomatic manifestations (difficulty in falling asleep, early awakening, difficulty in maintaining sleep, etc.) and psychological characteristics (anxiety, depression, sensitivity, etc.) and analyse the acupuncture effect for these symptoms of insomnia with short sleep duration.

# 2. Methods

## 2.1. Study design

This study is a randomized controlled trial with a single-centre, single-blind, 2×2 factorial design and will be completed in Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. The study period will be from November 2019 to April 2021, and the Shanghai Municipal Commission of Health and Family Planning will be the management organization of the study.

Insomnia subjects who meet the inclusion criteria will be divided into two groups according to the objective total sleep time (TST): insomnia with a short sleep duration group (objective sleep time < 6 h) and insomnia with a normal sleep duration group (objective sleep time ≥ 6 h). A total of 76 subjects will be recruited from each group. Each group will be randomly assigned to the acupuncture subgroup and the placebo acupuncture subgroup at a 1:1 ratio. The aim of this study is to evaluate the short-term

efficacy of acupuncture for the treatment of insomnia with short sleep duration. According to our previous research, each subject will experience screening, treatment and a follow-up period of approximately 8 weeks.

All subjects will complete the following scales [32]: The Pittsburgh Sleep Quality Index (PSQI) [33] and the Insomnia Severity Index (ISI) [34-35] will evaluate subjects' subjective sleep improvement. Subjects will be assessed for the objective total sleep time by actigraphy [36] in conjunction with a sleep diary [37]. Subjects' mood improvement will be evaluated by the Beck Anxiety Inventory (BAI) [38] and the Beck Depression Inventory (BDI) [39]. The Fatigue Severity Scale (FSS) [40] will be used to assess the improvement in fatigue. The above scales or actigraphy will be evaluated during the screening period and after the treatment at one-week and one-month follow-ups (Figure 1). PSG (NIHON KOHDEN, Japan) in this study will be used for screening purposes only. Subjects will sign the informed consent form after enrolment.

## 2.2. Participants

The study will include 152 insomnia participants. We plan to recruit participants in multiple ways, and the recruitment location will be restricted to Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine, Shanghai, China. Our hospital is a comprehensive tertiary hospital with clinical treatment, scientific research and teaching practice. The main source of the subjects will be the outpatients who meet our criteria. In addition, we will also recruit participants through newspapers, social media and advertising. The time limit will be from November 2019 to April 2021. The site of our clinical trial will be the Insomnia Diagnosis and Treatment Center of the Acupuncture and Moxibustion Department at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. All participants who are willing to participate in the trial will be required to call our research coordinator and arrange an outpatient interview on the first available date.

### 2.2.1. Inclusion criteria

The outpatient interview will be conducted in the form of a semi-structured interview questionnaire, which will contain the cause of insomnia, onset process, treatment process, main sleep complaints, bedtime status, sleep-wake cycle, other sleep-related symptoms, daytime symptoms, mental state, etc. [41]. The inclusion criteria have been developed based on the diagnostic criteria for chronic insomnia in the International Classification of Sleep Disorders (Third Edition) (ICSD-3) [42] developed by the American Academy of Sleep Medicine in 2014. The inclusion criteria are as follows:

(1) Between 18 and 65 years of age;

(2) Compliance with the diagnostic criteria for chronic insomnia in ICSD-3;

(3) Stable administration of sedative-hypnotic drugs for more than 3 months before entering the study or not taking such drugs;

(4) Meet all of the following: PSQI [33] > 5 points, ISI [34-35] > 14 points, BAI [38] < 45 points and BDI [39] ≤ 28 points;

(5) Never received acupuncture treatment;

(6) Voluntarily participated in the study and signed informed consent.

In addition, all participants will complete a one-week sleep actigraphy and diary to determine their sleep patterns and objective sleep duration before enrolment [43]. We will recruit 76 subjects in each group (insomnia with short sleep duration and insomnia with normal sleep duration). If one group completes recruitment first, that specific group will stop recruiting.

**2.2.2. Exclusion criteria**

The exclusion criteria are as follows:

(1) Severe hepatic and renal function damage, as well as haematologic diseases and respiratory diseases and diagnosis of mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [44];

(2) Semi-structured clinical interviews determine subjects have other sleep disorders rather than primary insomnia;

(3) Infectious diseases such as infectious hepatitis, tuberculosis, AIDS, and syphilis;

(4) Severe digestive system diseases and severe malnutrition;

(5) Pregnant or lactating;

(6) Severe trauma with no cure or not suitable for acupuncture, such as allergic constitution and severe dermatosis;

(7) An apnoea–hypopnea index (AHI) >10 or periodic limb movements index during sleep associated with >15 arousals per hour on diagnostic PSG [45];

(8) Participated in other clinical trials in the last 3 months.

## 2.3. Interventions

The acupuncturist for this study has received a master's degree in acupuncture and tuina at Shanghai University of Traditional Chinese Medicine, has 8 years of training experience, has obtained a doctor qualification certificate, and has 3 years of clinical work experience. All study participants will receive 10 days of training prior to the start of the trial to become more familiar with the process.

The subjects in the acupuncture group will be placed in the supine position. We have selected 5 acupoints for this study: GV20 (Baihui), PC 6 (Neiguan), SP 6 (Sanyinjiao),

HT 7 (Shenmen) and Ex-HN 1 (Sishencong). The reason for choosing these acupoints is the previous systematic review [46-47] and our clinical experience. A disposable sterile stainless steel acupuncture needle with a length of 40 mm and a diameter of 0.25 mm will be used (Andy, Guizhou, China). The acupuncturist will take the points on both sides of the body. The needle will be inserted into the skin to a depth of 10-20 mm, which is determined by the acupuncturist according to body type (high or short, fat or thin). After piercing, a thrusting and twirling of the needle will be performed to induce the sensation of "De qi", and the needle will be left for 20 minutes [48]. "De qi" means that after the needle has penetrated into the acupoint to a certain depth, the needle is thrust and twirled to cause the acupoint to obtain the induction of meridian qi. The subjects will have a self-conscious reaction such as soreness, heaviness or distention. This is the key process in acupuncture treatment [49].

Subjects who entered the control group will receive a placebo acupuncture treatment by using a non-invasive placebo needle [50] with the same acupoints as the treatment group. The Streitberger needle has been widely used in clinical research on placebo acupuncture treatment of insomnia [22,51-52], and studies have shown that using this needle in a placebo acupuncture group is reliable for the Chinese population [53]. Since the Streitberger needles will be in place for 20min, they will need to be firmly affixed to the skin or scalp. We have modified the procedure by using surgical tape (or hairpins in hairy regions) to hold the needles in place. This enables the needles to be applied in hairy regions and different needling directions to be attempted. Such a method has been adopted by mang other researchers [54].

Subjects from both the treatment group and the control group will be treated equally by the physician to prevent them from perceiving the difference. They will be informed about the acupuncture as follows: "In this study, different types of acupuncture treatment will be compared. One type is the usual acupuncture, and the other is associated with positive outcomes in previous clinical studies [55]." And subjects in both groups will be treated three times per week for 10 times by the same acupuncturist.

## 2.4. Outcome measures

### 2.4.1. Primary outcome measures

The PSQI consists of 19 self-evaluation items and 5 other evaluation items. The self-assessment items assess sleep quality, fall asleep time, total sleep time, sleep efficiency, concomitant symptoms, hypnotic drugs, and daytime functions. The total score is 0-21 points. Higher scores indicate worse sleep quality and more severe sleep disorders [33]. The PSQI is widely used in the clinic to assess sleep dysfunction [56], and it is more likely to assess an individual's sleep state on weekdays [57]. A total score > 5 indicates a need for clinical treatment [58]. The Chinese version of the PSQI has a high degree of reliability and validity for the Chinese population and can be used as an effective tool for sleep screening and evaluation in clinical and scientific research [59-60].

The ISI mainly evaluates the insomnia nature, insomnia severity, and effects of daytime function on patients. The scale is simple and easy to implement. It consists of 7 evaluation items with a total score of 0-28. The higher the score, the more serious the degree of insomnia [35]. It is mainly used for the screening of patients with insomnia and the evaluation of a therapeutic effect in clinical studies [61]. A total score of 8-14 indicates subclinical insomnia, and a total score > 14 indicates clinical insomnia. A change score of −8.4 points is associated with moderate improvement as rated by an independent assessor after treatment in the clinical sample [35, 62]. The Chinese version of the ISI is used in China's population assessment for insomnia with high reliability and validity [63].

### 2.4.2. Secondary outcome measures

The secondary outcome measures consist of (1) changes in the number of awakenings (NOA), total wake time (TWT), total sleep time (TST), and sleep efficiency (SE) measured by actigraphy before and after treatment; (2) changes in BAI, BDI, and FSS scores after treatment and during follow-up compared with before treatment; (3) changes in sleep onset latency (SOL), total wake time (TWT), total sleep time (TST), sleep efficiency (SE), and middle of the night wake after sleep onset (MWASO) from the sleep diary after treatment compared with those before treatment (Table 1).

ACT evaluates the body state by measuring the body movement by wearing a motion

sensor on the non-dominant wrist. It can be used as one of the objective indicators for evaluating sleep-wake state [36]. The motion watch 8 wrist ACT produced by CamNtech Ltd will be used in this study. Its acceleration sensitivity is <0.01 g, with 5 s as the analysis unit. The recorded sleep and activity data will be analysed by the corresponding MotionWare Software. The main parameters include sleep-wake parameters and rest-activity parameters. It can satisfactorily evaluate the four sleep indicators: number of awakenings, wake time after sleep onset, total sleep time, and sleep efficiency percentage [64]. Early studies have shown that ACT has a good fit to polysomnography (PSG) in assessing sleep and wakefulness (Rs = 0.52–0.71) and has a good sensitivity as an index of effect evaluation in insomnia treatment [65-66]. In this study, we will use ACT combined with a sleep diary [37] to record the sleep of the subjects for one continuous week. Changes in the number of awakenings (NOA), total wake time (TWT), total sleep time (TST), and sleep efficiency (SE) will be measured before and after treatment.

The BAI, which was developed by Beck in 1988 [67], contains a total of 21 different anxiety symptom items. It is used to evaluate the anxiety state of a subject in the past week. The higher the score, the more serious the degree of anxiety. Generally, BAI ≥ 45 is used as the criterion for positive anxiety. The scale is simple in content, easy in operation, and clear in understanding. The Chinese version has good reliability and validity. It is a commonly used measurement tool for anxiety symptom assessment in the Chinese population [68].

The BDI is based on the diagnostic criteria for depression in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. The first version was published in 1961 and revised to the current version by Beck et al. The scale has a total of 21 items that are used to evaluate the severity of a subject's depression over the past week. The higher the total score is, the more severe the depression. A total score of 0-13 is known as no depression, 14-19 as mild depression, 20-28 as moderate depression and 29-63 as major depression. The Chinese version has been tested and proven to have good reliability and validity [69].

The FSS [40] was formulated by Krupp in 1989. The scale has a total of 9 items and

is simple and easy to perform. A higher score indicates more severe fatigue. In insomnia patients, the FSS threshold is 5.5 points, and a high score represents the impaired daytime functional status of insomnia patients [70]. The Chinese version of this scale has been determined to have good reliability and validity [71].

**2.4.3. Safety assessments**

Safety will be assessed by routine blood test, renal function test and liver function test. These indicators are detected during the period of screening and after the treatment. We will still count the events during the trial through a list of adverse events. We will specifically evaluate them during the assessment phase [72] (Table 1). Adverse events will be defined as any adverse medical reactions that occurred from the time the subject signed the informed consent form to the time of the last follow-up, whether or not there is a causal relationship with the study treatment. Subjects are required to fill in the list of adverse events, which should record the time point, severity, measures taken, whether they are related to the treatment and prognosis. During the assessment phase, researchers will assess the possible relationship between adverse events and the study, as well as the combined medications. Adverse events include all adverse reactions that are definitely related to treatment, most likely related to treatment and likely related to treatment.

| Week | 0 | 1 | 2 | 3 | 4 | 8 |
|---|---|---|---|---|---|---|
| | Baseline | Treatment phase | | | | Follow-up phase |
| PATIENTS | | | | | | |
| Telephone reservation | × | | | | | |
| Enrolment | × | | | | | |
| Sign informed consent | × | | | | | |
| Clinical interview | × | | | | | |
| Sleep scales | × | | | | | |
| Physical examination | × | | | | × | |
| Laboratory test | × | | | | × | |
| PSG | × | | | | | |
| GROUPS | | | | | | |
| Acupuncture group (normal sleep duration) | | Ten treatments | | | | |
| Control group (normal sleep duration) | | Ten treatments | | | | |
| Acupuncture group (short sleep duration) | | Ten treatments | | | | |
| Control group (short sleep duration) | | Ten treatments | | | | |
| OUTCOME MEASUREMENT | | | | | | |
| PSQI | × | | | | × | × |
| ISI | × | | | | × | × |
| ACT | × | | | | × | |
| BAI | × | | | | × | |
| BDI | × | | | | × | |
| FSS | × | | | | × | |
| Sleep diary | × | × | × | × | × | |
| Success of subject-blinding test | | | | | × | |
| Adverse events | | | | | | |
| Reasons for dropouts or withdrawals | | × | × | × | × | × |
| Patient's compliance | | | | | × | × |

Note:

ACT: Actigraphy

BAI: Beck Anxiety Inventory

BDI: Beck Depression Inventory

FSS: Fatigue Severity Scale

ISI: Insomnia Severity Index

PSG: Polysomnography

PSQI: Pittsburgh Sleep Quality Index

Table 1. Trial processes chart

## 2.5. Sample size

According to previous literature [22], placebo acupuncture reduced the PSQI of chronic insomnia to 14.76 after treatment, and the standard deviation was 3.35. We hypothesize that the true acupuncture in our study could reduce the PSQI score by 2.2 points compared with the placebo acupuncture, and the standard deviation of 2.93 was taken from the previous research results. According to the needs of this study, we made α=0.05 and 1-β=0.90, according to the formula [73]:

$$n = \psi^2\left(\sum S_i^2/g\right)/\left[\sum\left(\overline{X_i} - \overline{X}\right)^2/(g-1)\right]$$

$\overline{X_1}$=12.56, $S_1$=2.93, $\overline{X_2}$=14.76, $S_2$=3.35, $\overline{X_3}$=12.56, $S_3$=2.93, $\overline{X_4}$=14.76, $S_4$=3.35, and $\overline{X}$=13.66; by looking up the table, $\psi$=2.17. Calculating the sample size of each group: n=30.92≈31; considering the loss factor (according to a 20% loss rate), the number of samples in each group is 38 cases, and the total number of samples in the 4 subgroups is 152 cases.

## 2.6. Randomization and blinding

The statistician outside the study will use SPSS 25.0 to generate two different sets of random numbers lists with 76 numbers in each. The random numbers in each list will be arranged in ascending order, with No. 1-38 for the control group and 39-76 for the acupuncture group. Subjects will enter the control group or the acupuncture group according to the random numbers corresponding to the order of signing the informed consent in a ratio of 1:1.

Random numbers and treatment protocols will be printed on the subject's treatment card and placed in an opaque envelope by an independent investigator. Each enrolled subject will be assigned to an order number and receive an envelope with their name on it. The acupuncturist will check whether the envelope was sealed and will open and remove the treatment card. During the trial, the generation of a random numbers list, subjects' recruitment, acupuncture treatment, outcome measures assessment, and follow-up will be performed independently by different researchers. Only the outside assistant and the acupuncturist will be aware of the allocation. Participants and other

relevant researchers will be blinded to the allocation.

The success of subject-blinding will be assessed by, at the end of the last treatment session, asking the subject if they believe they are receiving active treatment.

### 2.7 Data Collection and Management

Data will be collected at the baseline (one week before the first intervention), post intervention (at the end of intervention), one-week follow-up and one-month follow-up. Each visit will comprise three assessments: (1) subjects will complete sleep-related questionnaires independently in a private conference room at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. Completion of the questionnaires will require approximately 30 min; during this time, outcomes assessors will be available to answer questions; (2) subjects will complete a sleep diary at home under the guidance of outcome assessors; (3) subjects will undergo one-night PSG at the baseline, ACT before and after the intervention. Outcome assessors will be trained to promote participant retention, collect good quality data and complete follow-up. Data analysts will be trained on data entry, coding, security and storage. Statisticians in the research team will provide training on data assessment and analysis. Maintenance of participant confidentiality will be involved: (1) asking subjects only share personal and study-related information during our study; (2) storing data in the password-protected files on a designated specific computer with restricted access; (3) only the research-related person have access to personal identifiable information, which will be destroyed once the study is completed. Technical appendix, statistical code, and dataset available from the ResMan (www.medresman.org).

Subjects may withdraw from the study at any time for any reason. If any subject wishes to withdraw, the clinician will ask if they are willing to complete the final assessment and record the time of the last treatment. The incidence of withdrawal and loss to follow-up will be recorded and reported. We will also inquire the subjects about the reasons for absence, and will record compliance by the clinician.

### 2.8 Statistics and Analysis

The statistics and analysis of all data will be performed by two analytical researchers independent of the trial. Intention-to-treat (ITT) and per-protocol (PP) analysis will be used as evaluation methods to evaluate the final results of this study. Among them, ITT analysis will be used as the main analytical method. The multiple imputation method will be the primary method for processing the missing data, and an observation carried forward method will also apply to sensitivity analysis [74]. Data from dropout cases will be managed by both ITT analysis and PP analysis.

SPSS 25.0 will be used for statistical analysis. For the measurement data that conform to the normal distribution and homogeneous variance, the mean ± standard deviation will be used to describe the discrete tendency and central tendency. The comparison between the two groups will be performed by independent-samples t test. The comparison of multiple time points will be based on repeated measurement data combined with multivariate analysis of variance. Measurement data that do not conform to the normal distribution will be described by median, minimum, and maximum. The Mann-Whitney U rank sum test will be used for comparison between the two groups. The intra-group comparison will be based on the Friedman(F) rank sum test of the relevant samples.

The enumeration data will be expressed by frequency and constituent ratio. If the analysis index is two-category and multi-category unordered data, the comparison between groups will be performed by $\chi^2$ test. If the analysis index is hierarchical order enumeration data, the Mann-Whitney U rank sum test will be used for the intra-group comparison.

All statistical tests will be performed on a two-sided test, and $P \leq 0.05$ will be considered statistically significant.

## 3. Discussion

Some scholars have suggested that insomnia can be divided into two phenotypes

based on objective sleep duration, namely, insomnia with short sleep duration and with normal sleep duration. The former is an important phenotype of insomnia and has more serious health hazards [3-9]. At present, the treatment of insomnia tends to be biologically based (represented by benzodiazepine receptor agonists) and behaviourally based (represented by CBT-I). Most of the diagnosis and treatment guidelines of sleep disorders recommend CBT-I as the primary choice for treatment of insomnia and drug therapy as the secondary choice [11-13]. However, studies have shown that patients with insomnia with a short sleep duration are not sensitive to CBT-I treatment [14], these patients prefer to take sleep medicine. However, drug therapy has many adverse reactions, such as hangover effects, cognitive impairment and drug addiction [17-18]. It is important to seek safe and effective complementary and alternative medicine with few side effects. This is the basis of our research. Acupuncture treatment for insomnia provides such an opportunity.

In this study, our first purpose is to determine whether acupuncture has a therapeutic effect on insomnia compared with the placebo acupuncture group. Second, we will determine whether acupuncture has a curative effect on insomnia with short sleep duration. Finally, we will examine whether acupuncture treatment for two phenotypes of insomnia has a difference in efficacy.

In fact, past studies have not completely found a reliable method to properly define the insomnia phenotype, which is largely due to the lack of biomarkers for insomnia or objective indicators that can be used for classification. Some clinical practice guidelines do not recommend PSG as a diagnostic tool and a severity assessment tool for insomnia [75]. However, an increasing number of studies have shown that the use of objective sleep assessment tools to classify insomnia has a great effect on the analysis of many potential disease incidences [9-10,76]. This study provides further support for the use of an objective sleep index to help diagnose and treat the specific phenotypes of insomnia.

This study used actigraphy as a sleep time measurement tool and an objective assessment tool for sleep without introducing the PSG. Compared with actigraphy, PSG requires a bed rest time of approximately 8 h, but actigraphy does not have this limitation. By reviewing the previous literature comparing the differences between the

two measurement tools [65-66,77-78], actigraphy has a good fit to PSG in assessing the time of sleep and wakefulness in insomnia patients. However, to a certain extent, actigraphy is more likely to underestimate sleep maintenance time and overestimate the total arousal time, which may result in some of the subjects with a total sleep time > 6 h being included in the group of patients with insomnia with short sleep duration. However, first, the gap is small. Second, the conclusions of these differences under this inclusion criterion may represent a greater actual difference between the two phenotypes. In addition, using one-night PSG to evaluate the subject's objective sleep time has a first-night effect. Therefore, we chose a week of actigraphy data to assess the objective indicators. Moreover, previous studies have shown that actigraphy can be used as a useful and efficient tool to assess the sleep patterns of individuals in their own sleep environment [79-80].

The use of placebo control in acupuncture trials remains controversial [81]. In pharmacological treatment trials, an ideal placebo should be indistinguishable from the true interventions and be physiologically inert [82]. However, it remains a challenge to design an adequate placebo for non-pharmacological interventions, such as acupuncture, in which non-specific treatment will be exists in the placebo group [83]. Since placebo acupuncture can produce a significant non-specific therapeutic effects, there is little space left for the assumed specific effect of acupuncture [84]. Therefore, we expect that in the future research work, researchers will invent a more authoritative placebo acupuncture.

This study is the first trial to use acupuncture as an intervention to treat different phenotypes of insomnia. Our conclusions will expand the research results of previous studies and will further explain that insomnia with short objective sleep duration is a biologically more serious insomnia phenotype. These patients require more specific attention and more specific treatment options.

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## Author Contributions

CW and YFC conceived the research plan. CW and WJY drafted the protocol. XTY, CF, JJL and JW coordinated the study. WLX, YXZ and CW recruited the subjects. CW and WJY formed the analysis plan. All authors participated in, read and approved the final manuscript.

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## Competing interests

None declared.

## Patient and public involvement

Patients' priorities, experience and preferences were not involved in development of the research question and outcome measures, the design of this study, or the recruitment to and conduct of the study. The results will be not disseminated to study participants.

## Ethics approval

The trial has been approved by the ethics committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (No.: 2019-17).

## Provenance and peer review

Not commissioned; externally peer reviewed.

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**Fig.1. Trial flow chart**

HCG: Human chorionic gonadotropin

PSG: Polysomnography

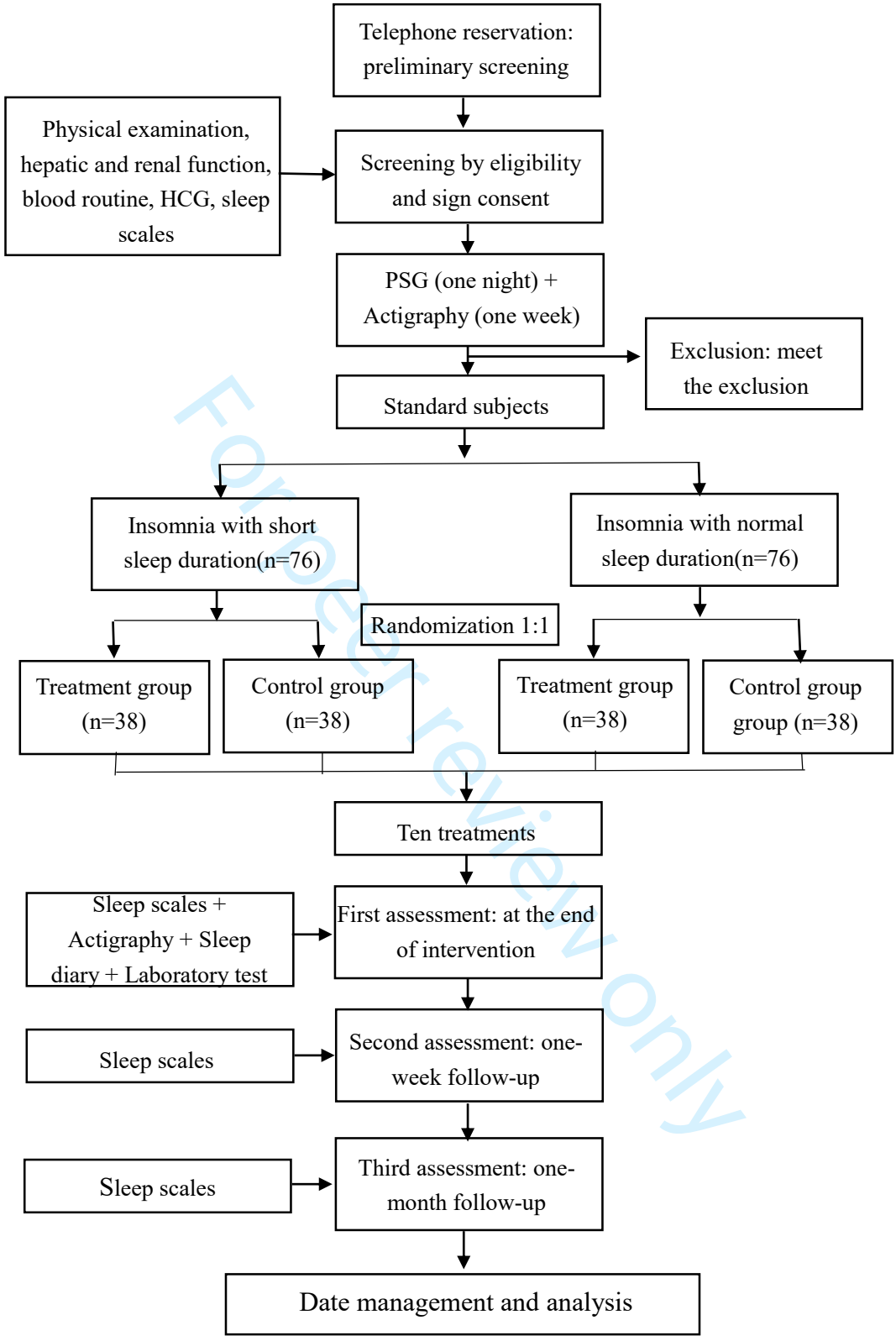


Fig.1. Trial flow chart

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 1 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | 1 |
| Protocol version | #3 | Date and version identifier | n/a |
| Funding | #4 | Sources and types of financial, material, and other support | 18 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 18 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | n/a |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | n/a |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |
| **Introduction** | | | |
| 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 | 3 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 3 |
| Objectives | #7 | Specific objectives or hypotheses | 4 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 4 |
| **Methods: Participants, interventions, and outcomes** | | | |
| 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 | 4 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will | 7 |

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| | | perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | n/a |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | n/a |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | n/a |
| 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 | n/a |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 6 |
| 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 | 13 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 14 |

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| 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 | 14 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 14 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 14 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 14 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 15 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 15 |
| 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 | 15 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 15 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | n/a |

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|---|---|---|---|
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | n/a |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | n/a |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| 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 | 11 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | n/a |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 19 |
| 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) | n/a |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | n/a |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 14 |

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| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 18 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | n/a |
| 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 | n/a |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | n/a |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |