Efficacy and Safety of Electro-Acupuncture (EA) on Insomnia in Patients with Lung Cancer: Study Protocol of a Randomized Controlled Trial

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Abstract
Background: Cancer-related insomnia (CRI) is one of the most prevalent complaints among cancer survivors and severely impairs patients’ quality of life. As a popular non-pharmacological alternative treatment, acupuncture provides a good clinical curative effect on insomnia. The aim of this trial is to evaluate efficacy and safety of electro-acupuncture on insomnia in patients with lung cancer.

Method: This is a protocol for a multicenter randomized single-blinded sham-controlled trial. We will randomly assign 252 eligible patients with lung cancer-related insomnia into two groups at a ratio of 1:1, the treatment group (EA) and the control group (sham EA). All treatment will be given 3 times per week for 8 weeks, and a 12-week follow-up will be conducted. The primary outcome will be measured by the Pittsburgh Sleep Quality Index (PSQI). The secondary outcomes will include sleep parameters recorded from the actigraphy, scores from Quality of Life Questionnaire Core-30 (QLQ-C30), and Patient Health Questionnaire-9 (PHQ-9). All adverse effects during the trial will be assessed by the Treatment Emergent Symptom Scale (TESS). The primary outcome will be assessed at baseline, week 4, week 8, week 12 and week 20. The secondary outcomes will only be assessed at baseline and week 8.

Discussion: This large-sample trial protocol will evaluate the efficacy of electro-acupuncture on insomnia in patients with lung cancer. This protocol, if proven to be effective, will contribute to filling the gap in treatment options in the CRI field and provide a promising intervention for insomnia in lung cancer survivors.

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http://www.chictr.org.cn/showproj.aspx?proj=44068

Background
Cancer-related insomnia (CRI) is one of the most prevalent complaints among cancer survivors, especially in the lung, breast, head and neck cancers[1]. Lung cancer has the highest prevalence of incidence and mortality of malignant tumors in China. It is expected that by 2020, the incidence of lung cancer will exceed 800,000 and the death toll will approach 700,000 in China[2] alone. According
to Wei’s research[3], the incidents of cancer-related insomnia among lung cancer patients has risen up to 68.4%. Concurrently, foreign researchers[4, 5] have shown that lung cancer patients have a relatively high incident rate of all sleep-related problems when compared with all other cancer types. The causative link between cancer survivors and increased incidents of insomnia remains uncertain, and may consist of complex interactions of various factors. Savard[6] divided the etiology into three main categories: predisposing, precipitating and perpetuating factors. Different pathological types and clinical stages also have significant effects on CRI as well as symptoms induced by cancer and adverse effects created by anti-cancer therapies. CRI is a frequently overlooked consequence of cancer diagnosis and treatment[7], mainly manifesting as difficulty in initiating sleep or maintaining sleep, waking up earlier than desired, and patient’s resistance to go to bed on an appropriate schedule. It results in negative effects, such as fatigue, attention impairment, irritability, daytime sleepiness, all of which severely impairs the overall quality of life and even prognosis of cancers[8]. Therefore, lung cancer-related insomnia is an important problem to be solved among the lung cancer survivors.

At present, pharmaceutical therapy is the most common therapy for management of insomnia with lung cancer, such as benzodiazepines (e.g. clonazepam, midazolam) and non-benzodiazepines (e.g. zolpione, zalepron). Although pharmacotherapy shows good short-term curative effect, long-term large doses are not recommended due to drug resistance, psychological dependence and physical dependence[9]. Meanwhile, the efficacy and safety of its interaction with anti-tumor drugs is not confirmed. Therefore, many patients refuse hypnotics, for they can impair the overall quality of life and even prognosis of tumors. In addition to pharmaceutical therapy, Cognitive Behavioral Therapy (CBT), exercise intervention and herbal medicine are applied in clinic as primary treatments, however, all lack valid evidence to confirm their efficacy and safety. Therefore, it is imperative to find a safe, effective therapy with few side effects, as currently, there is a dearth of effective methods to treat insomnia related to lung cancer.

As a popular non-pharmacological alternative treatment, acupuncture provides a good clinical curative effect on insomnia, takes effect quickly, and is relatively safe with few side effects. Previous
studies[10] have provided evidence that acupuncture has effects on sleep disorders in general population, but there are few high-quality studies focused on acupuncture as a method for the treatment of lung cancer-related insomnia. We will take the lead to prove the safety and efficacy of acupuncture as a treatment of insomnia in lung cancer patients. Otte[11] carried out a single group clinical trial, applying actigraphy as the main outcome measurement. After three sessions of acupuncture treatment, sleep duration and sleep efficiency were significantly improved among 10 breast cancer patients. There are two studies on the effects of acupuncture on depression symptoms[12] and hot flashes in cancer survivors[13] But it is uncertain that acupuncture has the curative effect on CRI, for that sleep-related measurement is only a secondary outcome in these studies. Song Jianrong[14] has carried out a large-sample randomized controlled trials of acupuncture on treatment of CRI, which divided into two groups: treatment group with acupuncture and control group that received estazolam and no acupuncture. The trial result showed that there were no statistical differences between the two groups in the sleep efficiency during the treating period. However, this trial exhibited some nullifying deficiencies, including such confounding factors as no restrictions to cancer types and no detailed refinement of inclusive criteria and treatment methods[15]. Therefore, rigorous high-quality and well-designed RCTs with large samples are urgently needed to prove the safety and efficacy of acupuncture treatment on insomnia in lung cancer patients. These contributions will lay a solid foundation for further promotion and application of acupuncture in the future.

The aim of this trial is to evaluate efficacy and safety of electro-acupuncture on insomnia in patients with lung cancer, and to explore the feasibility and preliminary effectiveness of electro-acupuncture on lung cancer-related insomnia using subjective questionnaires and objective sleep parameters. This protocol, if proven to be effective, will contribute to filling the gap of the CRI field and provide a promising curative intervention for lung cancer survivors with insomnia in clinic.

Methods
1. Study design
This is a study protocol of a multicenter randomized patient-and-assessor-blinded sham-controlled
clinical trial designed to evaluate the safety and efficacy of electro-acupuncture on insomnia in patients with lung cancer. A total of 252 eligible patients with lung cancer-related insomnia will be recruited from three hospitals in Shanghai: Shanghai Municipal Hospital of Traditional Chinese Medicine (TCM), Shanghai Chest Hospital, and Putuo District Central Hospital. Each participant will be informed of study-related information and sign a written informed consent before they enter the trial. They will then be randomly divided into treatment group and control group at a ratio of 1:1, receiving EA and sham EA 3 times per week for 8 weeks respectively. The schedule of enrollment, intervention and assessment is presented in Table 1. This trial is strictly designed to follow the Consolidated Standards of Reporting Trials (CONSORT) statement and Standards for Reporting Intervention in Controlled Trials of Acupuncture (STRICTA)[16] recommendations. The flowchart of the trial is presented in Fig. 1 and the study design schedule is presented in Table 1.

### Table 1

#### Study design schedule

| Period Week(W) | Enrollment | Allocation | Treatment | Follow-up |
|----------------|------------|------------|-----------|-----------|
| Week − 1       | ×          |            |           |           |
| Week 0         | ×          |            |           |           |
| Week 1         | ×          | ×          | ×         | ×         |
| Week 4         | ×          |            |           |           |
| Week 8         | ×          |            |           |           |
| Week 12        | ×          |            |           |           |
| Week 20        | ×          |            |           |           |

| Enrolment | Allocation | Treatment | Follow-up |
|-----------|------------|-----------|-----------|
| Informed consent | × |            |           |
| Medical history | × |            |           |
| Merger disease | × |            |           |
| Randomization | × |            |           |
| Intervention | × | ×          | ×         |
| Primary Outcome | × | ×          | ×         | ×         |
| PSQI | × | ×          | ×         | ×         | ×         | ×         |
| Secondary outcomes | | | | |
| Actigraphy | × |            |           |           |
| OQLQ-C30 | × |            |           |           |
| PHQ-9 | × |            |           |           |
| Dose of hypnotics | × | ×          | ×         | ×         | ×         | ×         |
| Adverse event monitoring (side effects and complications) | × | ×          | ×         | ×         | ×         | ×         | ×         |
| Assessment of credibility | × |            |           |           |
| Assessment of blinding success | × |            |           |           |

#### 2. Participants

#### 2.1 Recruitment
This multicenter randomized controlled trial will be conducted in Shanghai Municipal Hospital of Traditional Chinese Medicine (TCM), Shanghai Chest Hospital, and Putuo District Central Hospital. We plan to recruit 252 participants in total through online and offline advertisement inside and outside these hospitals. Patients who have interest in entering this trial can phone the researchers or communicate with them face to face for more study details. The researchers will screen patients according the inclusion and exclusion criteria, and then thoroughly inform the patients of benefits gained from this trial and potential adverse reactions. Eligible participants will be asked to sign written informed consent before proceeding with the intervention and assessments.

2.2 Inclusion criteria

1. Male or female patients aged between 19 to 70 years old;
2. Diagnosed with stage I-IIIA pulmonary malignancy according to imaging result, histologic examination and TNM classification;
3. Continuous insomnia related to lung cancer treatment or cancer itself for at least 3 months, and meets the diagnostic criteria of chronic insomnia according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), American Psychiatric Association (APA);
4. An Eastern Cooperation Oncology Group (ECOG) performance status of less than 2;
5. Score of Pittsburgh Sleep Quality Index (PSQI) of more than 11;
6. Have never received acupuncture treatment;
7. Willing to participate in the trial and provide written consent;

2.3 Exclusion criteria

1. A plan for surgery or chemotherapy during the trial;
2. A diagnosis of secondary insomnia caused by depression, anxiety or other psychiatric disorders and addition of caffeine, alcohol or drugs;
3. Index of cancer pain measured by the numeric rating scale ≥ 4;
4. A diagnosis of severe cognitive deficit failing to cooperate;
5. A diagnosis of severe diseases of the cardiovascular, hepatic, renal, cerebrovascular, or hematopoietic systems;
6. Acupuncture area with skin infection, ulcer and soars;
7. Pregnant or breastfeeding women;
8. Having participated in other clinic trials within 4 weeks of the beginning of this trial;

2.4 Randomization and allocation concealment

This trial will adopt stratified, variable block randomization method with setting a random block size as 2, 4 or 6. An independent researcher, who has no contact with participants, assessors and acupuncturists, will use SPSS (version 24.0) to generate random numbers with the randomized blocks, dividing 252 participants into two groups at a ratio of 1:1: treatment group and sham group, and randomly allocate them into three different hospitals: Shanghai Municipal Hospital of Traditional Chinese Medicine (TCM), Shanghai Chest Hospital, and Putuo District Central Hospital. The researcher will make random allocation cards, each with its allocated hospital and group recorded, and seal each card into an opaque envelope, which will not be revealed until the first acupuncture treatment.

2.5 Blinding

This is a single-blinded (patient-assessor-blinded) study. Before treatment, all participants will be informed that they will be assigned to either EA group or sham EA group. They will also be required to wear eye-patch in a private quiet space during the whole treatment period. The principal researcher, assistant researchers, data analysts, assessors and statisticians will all be blinded to the group allocation. Only the acupuncturist will know their allocated groups, but they will not be informed of any qualitative information on the patient, including severity of lung cancer-related insomnia, merger disease, or dose of hypnotics. This trial will set up a data safety monitoring committee according to the guidance of Data Safety Monitoring Board (DSMB). Experts in the committee will be responsible for monitoring the data safety and have the right to reveal blinded data.

3. Interventions

Participants will receive either EA or sham EA, three times per week for eight weeks, and the follow-
up period will be three months. Only a licensed acupuncturist with more than two years of clinical experience will be responsible for performing the real and sham acupuncture treatment. All manipulation should adhere to the STRICTA. Every treatment session will last for 30 minutes in a private quiet space, with each participant wearing an eye-patch and in a lying position.

3.1 Electro-acupuncture (EA) Treatment

Participants in treatment group will receive real electro-acupuncture treatment. Stainless steel 0.25*40 mm acupuncture needles (Wuxi Jiajian Medical Material Co., Ltd., Wuxi, China) will be inserted into 15 acupoints, including 11 core acupoints and 4 additional acupoints. The core acupoints are GV20 (Baihui), GV24 (Shenting), GV29 (Yintang), bilateral EX-HN22 (Anmian), HT7 (Shenmen), SP6 (Sanyinjiao), ST36 (Zusanli) and the additional acupoints should be chosen from the following points: LR3 (Taichong), KI3 (Taixi), PC6 (Neiguan), CV4 (Guanyuan), CV12 (Zhongwan), LR14 (Qimen), ST44 (Neiting), LR2 (Xingjian), based on syndrome differentiation of participants. The locations, indications, and manipulation methods are specifically presented in Table 2. After the needle is inserted to a certain depth of points, it will be manipulated with needling techniques including lifting and thrusting or rotating methods for Deqi sensation. After Deqi, the electro-acupuncture device (CMNS6-1, Wuxi Jiajian Medical Device Co., Ltd., China) will be applied connecting to points GV20 (Baihui), and GV29 (Yintang), bilateral SP6 (Sanyinjiao) and ST36 (Zusanli) with 3 Hz frequency and the varying amplitude depending on the comfort of the participant which will been limited between 2 to 5 mA, to strengthen the needling sensation.

3.2 Sham EA Control

Participants in the control group will receive sham electro-acupuncture treatment at the same acupoints as the treatment group with a blunt tipped placebo needle manufactured in Germany[17]. This kind of needle can move inside the handle and appear to be shortened after puncturing without penetrating the skin. Participants will find it difficult to distinguish the placebo needle and real acupuncture needle because of the similar sensation and appearance. The electro-acupuncture device will be connected to points, GV20, GV29, bilateral SP6, and ST36 without any electrical current.
Table 2
Location, indication and methods of acupoints for treating lung cancer-related insomnia

| Acupoints   | Location | Indication | Method                                      |
|-------------|----------|------------|---------------------------------------------|
| GV20 (Baihui) | 5 cun directly above the midpoint of the anterior hairline, at the midpoint of the line connecting the apexes of the two auricles. | Subcutaneous insertion 16–26 mm. Moxisibustion can be used for reinforcing Yang. |
| GV24 (Shenting) | 0.5 cun directly above the midpoint of the anterior hairline. | Subcutaneous insertion 16–26 mm. |
| GV29 (Yintang) | On the forehead, at the midpoint between the two medial ends of the eyebrow. | Subcutaneous insertion 10–16 mm. |
| EX-HN22 (Anmian) | At the midpoint between Fengchi and Yifeng., at the middle of sternocleidomastoid tendon. | Perpendicular insertion 33–49 mm. |
| HT7 (Shenmen) | At the ulnar end of the transverse crease of the wrist, in the depression on the radial side of the tendon of m. flexor carpi ulnaris. | Perpendicular insertion 10–16 mm. |
| SP6 (Sanyinjiao) | 3 cun above the medial malleolus, on the posterior border of the medial aspect of tibia. | Perpendicular insertion 33–49 mm. |
| ST36 (Zusanli) | 3 cun below Dubi (ST35), one finger-breath(middle finger)from the anterior crest of tibia. | Perpendicular insertion 33–66 mm |
| LR3 (Taichong) | On the dorsum of the foot, in the depression proximal to the first metatarsal space. | Perpendicular insertion 16–26 mm |
| PC6 (Neiguan) | 2 cun above the transverse crease of the wrist, on the line connecting Quze(PC3) and Daling(PC7), between the tendon of m. palmaris longus and m. flexor carpi radialis. | Perpendicular or oblique insertion 16–33 mm. |
| KI3 (Taixi) | Posterior to the medial malleolus, in the depression between the tip of the medial malleolus and tendon calcaneus. | Perpendicular or oblique insertion 16–33 mm |
| CV4 (Guanyuan) | On the anterior midline, 3 cun below the umbilicus. | Perpendicular or oblique insertion 33–40 mm. This point is often used for moxibustion for tonification. |
| CV12 (Zhongwan) | On the anterior midline, 4 cun above the umbilicus. | Perpendicular or oblique insertion 33–40 mm. |
| LR14 (Qimen) | Directly below the nipple, in the sixth intercostal space, 4 cun lateral to the anterior midline. | Oblique or subcutaneous insertion 16–26 mm |
| ST44 (Neiting) | Proximal to the web margin between the second and third toes, at the junction of red and white skin. | Perpendicular or oblique insertion 16–26 mm |
| LR2 (Xingjian) | On the dorsum of the foot, proximal to the margin of the web between the first and second toes. | Perpendicular or oblique insertion 16–26 mm |

4. Outcome measures

4.1 Primary outcome measure

The primary outcome will be the mean changes in Pittsburgh Sleep Quality Index (PSQI) in week eight when compared to the baseline. As the most rigorously validated sleep healthy assessment tool, PSQI is a self-rated questionnaire used to assess sleep quality and disturbance over a 1-month time interval. It consists of 24 items to be rated, 19 of which are self-reported and 5 of which are require
secondary feedback from a room or bed partner[18]. The seven components include: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficacy (SE), sleep disturbance, use of sleeping medication, and daytime dysfunction. The sum of the individual component scores create one total score (range 0-21). The higher score indicates a worse sleep quality and more severe sleep disorder and vice versa.

4.2 Secondary outcome measures

4.2.1 Actigraphy

Actigraphy is an objective, non-intrusive method for estimating sleep-wake patterns using activity-based monitoring[19]. Computer-based software is interfaced with devices to provide automatic measurements for certain variables recorded in the Actigraphy, such as sleep duration, sleep efficiency, and bedtime onset.

4.2.3 Quality of Life Questionnaire Core 30 (QLQ-C30)

Quality of Life Questionnaire Core 30 (QLQ-C30) is created by the Quality of Life Group from the European Organization for Research and Treatment of Cancer (EORTC), specifically for the purpose of assessing various aspects related to health, disease, and treatment for cancer patients. It is composed of 30 items, divided into five functioning domains, three symptom domains, one domain that evaluates overall quality of life, five single domain and one separate domain to evaluate financial impact[20]. For the functioning domain and overall quality, the higher scores indicate the better quality of life, conversely, for the symptom domain a higher score indicates a worse quality of life.

4.2.4 Patient Health Questionnaire-9 (PHQ-9)

The Patient Health Questionnaire-9 (PHQ-9), as a 9-item self-administered depression screening and diagnostic tool, is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) depression symptom criteria. PHQ-9 is used to assess depression conditions during the initial 2 weeks. The final summed scores range from 0 (no depressive symptom) to 27 (all symptoms occurring daily) [21].

4.3 Other measures

4.3.1 Dose of hypnotics
Given participants’ psychological condition, oral intake of hypnotics will be allowed to alleviate their insomnia symptoms. Hypnotics will not be restricted but the name and dosage of drug must be recorded precisely on CRF, especially when the dosage is increased or decreased.

4.3.2 Safety assessment

Any adverse events (AEs) will be observed, those which are deemed to be unfavorable or unintended signs, symptoms, or diseases occurring due to the acupuncture or the hypnotics intake should be dealt with according to the protocol. The type of AEs and severity will be recorded in the CRF, including continuous needling pain, local hematoma, infection, discomfort, palpitation, or dizziness during and after the treatment. If a severe adverse event (SAE) occurs, they should be reported to the researchers and the Ethics Committee in detail within 24 hours after the occurrence and be assessed by the Treatment Emergent Symptom Scale (TESS) for further evaluation and management. And then the Ethics Committee will deliver the solution to DSMB, who retain the right to terminate the trial at any point. Researchers will pay sustained attention to participants who experience any AEs until it has been resolved, especially to those who have withdrawn the trial due to the AEs.

4.3.3 Assessment of credibility

In this trial, the credibility assessment from an article by Charles Vincent[22] is particularly applied to assess the reliability and credibility in the controlled trials of acupuncture and other physical therapies. The questions presented to the participants for rating on a 6 point scale are as follows: 1. How confident do you feel that this treatment can alleviate your complaints? 2. How confident would you be in recommending this treatment to a friend who suffered from similar complaints? 3. How logical does this treatment seem to you? 4. How successful do you think this treatment would be in alleviating other complaints?

4.3.4 Assessment of the subject blinding success rate

All participants will receive the blinding test twice in week 1 and week 8 to assess the success rate of subject blinding. The question is “When you are volunteered for the trial, you were informed that you have the equal chance of receiving traditional acupuncture and acupuncture-like stimulation treatment. Which one do you think you have received? ” Participants should choose one of the three
answers: acupuncture treatment, acupuncture-like stimulation treatment, or uncertain.

5. Statistical methods

5.1 Sample size estimation

The calculation of sample size is based on the review of acupuncture for insomnia[10]. Referring to this study, the mean difference of PSQI between two groups is assumed to be 2.0 with standard deviation of 4.36 for the both groups. Through PASS system (version 15.0.5) calculating, a sample size of 202 can provide 90% power to reject the null hypothesis with a significance level of 0.05 using a two-side two-sample T-tests assuming equal variance. Considering the expected dropout rate of 20%, the final sample size is 252, 126 for each group.

5.2 Data collection and management

Data will be collected in the CRF by the assessors after acquiring the signed consent from participants. To guarantee the consistency of data, two research coordinators will double-enter and check data from CRF once a week. To promote participants retention, and prevent their loss, assessors will make phone calls during a 3-month follow up.

5.3 Statistical analysis

A full analysis set (FAS) is based on ITT principle, that is including all the qualified participants who meet the inclusion criteria, who receive the intervention at least once, and who provide outcome assessment at least once. In statistical analysis, any the missing primary outcome will be replaced by the data from last time point according to ITT principle. A Per-Protocol Set (PPS) will be used to analyze those who completed the trial without a major violation of the protocol[23]. A Safety Analysis Set (SAS) is based on the principle of exposure to observe safety indicators for any participants received the intervention at least once. Data analyses will be performed with the statistical software SPSS (version 24.0). A two-sided significance level will be set at 5% and missing data will be rectified by using ITT principle.

The null hypothesis is that the outcome of the treatment group is the same as the control group, while the alternative hypothesis is that the treatment group see a significant difference in outcome from the control group. The main objective is to compare the mean change of PSQI at week 8
between treatment group and the control group. Continuous data will be represented by average, standard deviation, median, minimum value and maximum value, whereas categorical data will be represented by percentages. A paired-sample T test will be used when comparing all continuous outcomes at different time points to the baseline. For comparison of two independent samples, the analysis of covariance (ANCOVA) will be used for primary outcome PSQI if the residual are normally distributed, a t-test for other continuous data and a chi-square test for categorical data[24]. If the residual are normally distributed, a non-parametric test will be used for both continuous and categorical data. For the equilibrium analysis of baseline values, a t test or chi-square test will be used to compare demographic data and other basic values to measure the equilibrium between two groups.

6. Quality control
To guarantee the quality of this trial, all acupuncturists and assessors are licensed doctors and will be required to receive standard training from three hospitals prior to the beginning of the trial. The training program includes recruitment, interventions, and detailed assessment process. An independent Data and Safety Monitoring Board (DSMB) will be established to supervise whether the study design meets the standard guide, and guarantee the accuracy of this trial. The committee consist of five members in different fields: Professor Lixing Lao in acupuncture from Virginia University of Integrative Medicine, Professor Jijun Wang in psychology from Shanghai Mental Health Center, Professor Ruiping Wang in statistics form Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Professor Lixin Wang and Professor Peng Zhang in oncology from Shanghai Pulmonary Hospital, who all have to declare no conflict of interest in this study. DSMB is responsible for monitoring data, identifying problems, examining collected data, and controlling bias. Once they find there existing any problems or severe adverse events during the trial, they have the right to suspend the trial until the problem has been solved or even terminate it at any point.

Discussion
Nowadays, acupuncture therapy has been widely used in clinical practice as a popular non-pharmacological alternative treatment for insomnia, as more and more research has shown its
efficacy and safety. However, most studies focus on acupuncture for general insomnia and there are fewer high-quality studies about acupuncture on treating CRI among lung cancer patients. Thus, it is expected that this study will contribute to adding more strong evidence for the effectiveness of acupuncture for CRI.

The main purpose of this trial is to present a well-designed multicenter randomized single-blinded sham-controlled trial to evaluate the efficacy and safety of electro-acupuncture for insomnia in patients with lung cancer. Despite their advantages, previous researches related to CRI have some limitations, including inexact inclusion criteria, substandard study design, unpractical methods and indefinite factors decreasing quality of insomnia among lung cancer patients. Firstly, we design this trial with two groups, EA and sham EA to identify whether it is real electro-acupuncture that plays a role in treating insomnia in lung cancer patients or it is just the placebo effect. We will limit the inclusion criteria to specific cancer type, ongoing cancer therapy, and tailor points selection for each patient. Secondly, given participants’ psychological condition, oral intake of hypnotics is allowed to alleviate their insomnia symptoms and ensure that each participant gains the optimum benefit from this trial. Thirdly, we will apply semi-standard point selection, composed of core acupoints and additional acupoints, with reference of acupuncture literature and the acupuncturists’ clinical experiences. From additional acupoints, only four of them will be chosen according to specific symptoms of participants, strictly following standardization of syndrome differentiation and treatment administration of TCM. All acupoints will be located with reference to the International Standard Library of Chinese Medicine[25]. Finally, this trial will apply both objective and subjective outcomes representing sleep quality and the related symptoms among lung cancer patients. Most of the acupuncture studies on insomnia have used only patient-reported outcomes, furthermore, a small number of studies using objective outcomes such as actigraphy to show consistent results on the effects of acupuncture[23]. We intend to compare the difference between objective and subjective outcomes and unearth more thought-provoking questions based on the outcomes in this trial.

Although this trial is designed to address the limitations in previous trials, some potential issues still remain. Firstly, to ensure the successful implementation of sham EA techniques, acupuncturists will
accept training before the beginning of the trial and prepare to reasonably educate the patients through systematically studying and mastering a solid foundation of knowledge about lung cancer-related insomnia. Secondly, to ensure compliance from patients, we will strengthen the public education of medical knowledge to patients and improve their quality of life in all relevant aspects. For instance, we will make reasonable arrangements for treatment time and consultation time by phone or e-mail to increase their attendance rate and free acupuncture treatment will be promised by acupuncturists if the patients are not satisfied with the results of their treatment during the trial[26].

To sum up, in this trial, we will standardize point selection, manipulation, assessment and therapists’ clinical experience following the CONSORT statement and STRICTA recommendations rigorously. We expect this study will confirm the efficacy and safety of acupuncture on insomnia in patients with lung cancer, contributing to filling the gap of the CRI field and providing a promising curative intervention for lung cancer survivors with insomnia in clinic.

Trial status
The version number of this protocol is 1.0, dated on 1 April, 2019. The clinical trial is in preparation at present. The recruitment will begin on 1 May, 2020, and be completed in late 2022 as scheduled.

Abbreviations
EA: Electro-acupuncture; CRI: Cancer-related insomnia; PSQI: Pittsburgh Sleep Quality Index; QLQ-C30: Quality of Life Questionnaire Core-30; PHQ-9: Patient Health Questionnaire-9; TESS: Treatment Emergent Symptom Scale; CBT: Cognitive Behavioral Therapy; TCM: Traditional Chinese Medicine; CONSORT: Consolidated Standards of Reporting Trials; STRICTA: Standards for Reporting Intervention in Controlled Trials of Acupuncture; DSM-V: The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; APA: American Psychiatric Association; ECOG: Eastern Cooperation Oncology Group; DSMB: Data Safety Monitoring Board; SE: sleep efficacy; EORTC: European Organization for Research and Treatment of Cancer; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders; CRF: case report forms; AEs: adverse events; SAE: severe adverse event; FAS: full analysis set; ITT: intention-to-treat principle; PPS: Per-Protocol Set; SAS: Safety Analysis Set; ANCOVA: analysis of covariance.

Declarations
Ethics approval and consent to participate
This trial has been approved by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine (2019SHL-KY-08) with the Helsinki Declaration. An additional file shows this in more detail [see Additional file 1]. Before enrollment, each participant will be clearly aware of the purpose, procedure and the potential risk of this trial and then give their written informed consent.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Author’s contributions**

SFX, HYY and SSL conceived the study. HYY, SZ, HGW drafted the protocol. YL, ZHF, MZ, SFX, XLC, XFZ, MH, LLW, TTL participated in the design of the study and contributed to the refinement of the protocol. WZ was responsible for the statistical design of the study. SFX, ZJZ, XY, SSL provided clinical advice and made critical revisions. SFX is a principal investigator of the study and has the final responsibility for the decision to submit this manuscript for publication. All authors read and approved the final manuscript.

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Figures
Recruitments

Screening

Ineligible subjects excluded

Baseline assessment (week 0)

Randomization (1:1)

Treatment group (N=126)
EA 3 times per week for 8 weeks

Control group (N=126)
Sham EA 3 times per week for 8 weeks

Shanghai Municipal Hospital of TCM;
Shanghai Chest Hospital;
Putuo District Central Hospital

Assessment at week 4 → PSQI

Assessment at week 8

Assessment at week 12

Assessment at week 20

Data collection and analysis

Figure 1

Study flowchart
Supplementary Files
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